

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-393 & 21-394**

**ADMINISTRATIVE**  
**DOCUMENTS/CORRESPONDENCE**

## EXCLUSIVITY SUMMARY

NDA # 21-393

SUPPL #

HFD # 560

Trade Name Advil PM Liqui-Gels

Generic Name 200 mg ibuprofen and 25 mg diphenhydramine hydrochloride

Applicant Name Wyeth Consumer Healthcare

Approval Date, If Known

### 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

N/A

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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES  NO

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

3 years

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?

N/A

**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#



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:

AE-97-01: Advil PM Pilot Oral Surgery Study; pilot study  
AE-98-01: Advil PM Oral Surgery Study I, efficacy and safety  
AE-98-02: Advil PM Oral Surgery Study II; efficacy and safety  
AE-98-03: Advil PM Oral Surgery Does-Response Study  
AE-98-04: Advil PM Inpatient Headache Study  
AE-97-08: Advil PM Maximum Use Safety and Efficacy Study  
AE-04-14A: Advil PM Oral Surgery Study Using Actigraphy

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

- AE-97-01: Advil PM Pilot Oral Surgery Study; pilot study
- AE-98-01: Advil PM Oral Surgery Study I, efficacy and safety
- AE-98-02: Advil PM Oral Surgery Study II; efficacy and safety
- AE-98-03: Advil PM Oral Surgery Does-Response Study
- AE-98-04: Advil PM Inpatient Headache Study
- AE-97-08: Advil PM Maximum Use Safety and Efficacy Study
- AE-04-14A: Advil PM Oral Surgery Study Using Actigraphy

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 56,521      YES       ! NO   
! Explain:

Investigation #2  
IND # 56,521      YES       ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not

identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

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:

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Name of person completing form: Leah Christl

Title: Regulatory Project Manager

Date: December 19, 2005

Name of Office/Division Director signing form: Charles Ganley

Title: Director, Office of Nonprescription Products

**APPEARS THIS WAY  
ON ORIGINAL**

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/s/

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Charles Ganley  
12/19/2005 11:51:23 AM

**ITEM 16:     DEBARMENT 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.

WYETH CONSUMER HEALTHCARE

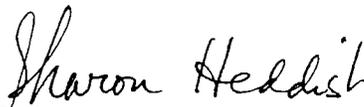


Director  
Global Quality Assurance and Compliance

**ITEM 16: DEBARMENT STATEMENT**

Whitehall-Robins Healthcare hereby certifies that it did not and will not use in any capacity the services of any person debarred under Sections 306 of the Act in connection with such application.

WHITEHALL-ROBINS HEALTHCARE



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Sharon C. Heddish  
Vice President  
Regulatory Affairs, Worldwide

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-393 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: 16-OCT-2001 Action Date: 27-DEC-05 PDUFA Goal Date \_\_\_\_\_

HFD 560 Trade and generic names/dosage form: Advil PM Liqui-Gel (200 mg ibuprofen and 25 mg diphenhydramine hydrochloride capsules)

Applicant: Wyeth Consumer Healthcare Therapeutic Class: 5030300

Indication(s) previously approved:

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: For relief of occasional sleeplessness when associated with minor aches and pains

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 0 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 12 Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 12 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 18 Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 21-393  
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 12-22-03)

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/s/

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Leah Christl

12/19/2005 10:51:54 AM



# OTC Drug Labeling Review for ADVIL PM - Addendum

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

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**SUBMISSION DATE:** December 14 and 15, 2005 (via e-mails)      **RECEIVED DATE:** December 14 and 15, 2005 (via e-mails)

**REVIEW DATE:** December 14 and 15, 2005

**NDA/SUBMISSION TYPE:** NDA 21-393 (Advil PM Liquigels)  
21-394 (Advil PM Caplets)

**SPONSOR/CONTACT:** Wyeth Consumer Healthcare  
5 Giraida Farms  
Madison, NJ 07940  
Tel: 973-660-5825

**DRUG PRODUCT:** Advil PM

**ACTIVE INGREDIENT:** Liquigels : Ibuprofen, 200 mg/  
Diphenhydramine HCl 25 mg  
Caplets : Ibuprofen 200 mg/ Diphenhydramine  
citrate 38 mg

**INDICATIONS:** Pain reliever and Nighttime sleep-aid

**PHARMACOLOGICAL CATEGORY:** Internal analgesic/nighttime sleep-aid

**LABELING SUBMITTED:** 20 counts container and carton label, and 2-count professional pouch dispenser for caplets and 32 counts carton and blister label, 4-counts gravity feed dispenser and shelf tray for liquigels as representative labels

**REVIEWER:** Marina Chang, R.Ph.

## BACKGROUND

In response to a discipline review letter dated December 9, 2005, the sponsor submitted representative labeling revisions to the following:

- A. Caplet: 20 counts container and carton label for caplets as representative labeling for 20, \_\_\_\_\_ counts and 2-count pouch and professional pouch dispenser (50 packets of 2).
- B. Liquigel: 32 counts carton and blister label, 4-counts gravity feed dispenser and shelf tray.

## REVIEWER'S COMMENTS

The labeling submitted for this NDA is in accordance with FDA's discipline review letter dated December 9, 2005. The sponsor also included the cardioprotection warning statement identical to the warning statement the Agency provided on December 5, 2005 in a separate communication. (Wyeth formally accepted this warning statement in its correspondence of December 6, 2005 to a separate application.) The sponsor indicated that the labeling submitted is representative of other package sizes for Advil PM Caplets/Liquigels. The only revisions to these representative labels will be the declaration of net quantity of content statement to reflect each package size.

## RECOMMENDATIONS

The representative carton and container/blister labels submitted for these applications can be approved, request the sponsor to submit final printed labeling for all marketing SKUs, identical to the representative labeling, except the declaration of net quantity of content statement to reflect the packaging size, submitted on December 14, 2005, when available.

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/s/

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Marina Chang  
12/19/2005 08:44:21 AM  
INTERDISCIPLINARY

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST		
NDA 21-393	Efficacy Supplement Type SE-	Supplement Number
Drug: Advil PM Liqui-Gels		Applicant: Wyeth Consumer Healthcare
RPM: Leah Christl		HFD-560      Phone # 301-796-0869
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)          (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><b>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</b></p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		4 New combination
• Other (e.g., orphan, OTC)		OTC
❖ User Fee Goal Dates		December 27, 2005
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid   UF ID number 4158
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



(Note: This can be determined by confirming whether the Division has received a written notice from the 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 box below (Exclusivity).*

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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).

*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 box below (Exclusivity).*

*If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>• Exclusivity summary</li> <li>• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	No
<ul style="list-style-type: none"> <li>• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? 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.</li> </ul>	<input type="radio"/> Yes, Application # _____ <input checked="" type="radio"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	

<b>❖ Actions</b>	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	AE 08-AUG-2002 AE 18-DEC-2003
• Status of advertising (approvals only)	<input type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
<b>❖ Public communications</b>	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
<b>❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</b>	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
<b>❖ Labels (immediate container &amp; carton labels)</b>	
• Division proposed (only if generated after latest applicant submission)	<input checked="" type="checkbox"/> December 14 & 15, 2005
• Applicant proposed	<input checked="" type="checkbox"/> October 16, 2001
• Reviews	<input checked="" type="checkbox"/> July 25, 2002; November 4, 2005; December 19, 2005
<b>❖ Post-marketing commitments</b>	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	
<b>❖ Outgoing correspondence (i.e., letters, E-mails, faxes)</b>	<input checked="" type="checkbox"/> See Outgoing Correspondence tab
<b>❖ Memoranda and Telecons</b>	<input checked="" type="checkbox"/> See Memos to the File and Telecons tab
<b>❖ Minutes of Meetings</b>	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	December 1, 2000
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
<b>❖ Advisory Committee Meeting</b>	
• Date of Meeting	
• 48-hour alert	
<b>❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)</b>	<b>Not applicable</b>

<b>Summary Reviews</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	Office Director Memorandum December 19, 2005
<b>Clinical Review Cycle</b>	
❖ Clinical review(s) <i>(indicate date for each review)</i>	November 4, 2005; October 21, 2005
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	Not applicable
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	Refer to November 4, 2005 Clinical Review
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	Not applicable
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	(X) see Pediatric Page tab December 19, 2005
❖ Demographic Worksheet <i>(NME approvals only)</i>	Not applicable
❖ Statistical review(s) <i>(indicate date for each review)</i>	December 1, 2005
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	September 19, 2005; December 7, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	Not applicable
❖ Clinical Inspection Review Summary (DSI)	None
• Clinical studies	
• Bioequivalence studies	
<b>Environmental Review Cycle</b>	
❖ CMC review(s) <i>(indicate date for each review)</i>	Prior review cycle
❖ Environmental Assessment	Prior review cycle
• Categorical Exclusion <i>(indicate review date)</i>	Prior review cycle
• Review & FONSI <i>(indicate date of review)</i>	Prior review cycle
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	Prior review cycle
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	Prior review cycle
❖ Facilities inspection (provide EER report)	Date completed: <b>Prior review cycle</b> ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed <b>Prior review cycle</b> ( ) Requested ( ) Not yet requested
<b>Nonclinical Review Cycle Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	Prior review cycle
❖ Nonclinical inspection review summary	Not applicable
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	Not applicable
❖ CAC/ECAC report	Not applicable

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/s/

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Leah Christl

12/19/2005 03:25:54 PM



NDA 21-393  
NDA 21-394

**DISCIPLINE REVIEW LETTER**

Wyeth Consumer Healthcare  
Attention: Mary Davis  
Director, Regulatory Affairs  
5 Giralda Farms  
Madison, NJ 07940

Dear Ms. Davis:

Please refer to your October 16, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil PM Liqui-Gels (200 mg ibuprofen/25 mg diphenhydramine HCl capsules).

Please refer to your October 16, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil PM Caplets (200 mg ibuprofen/38 mg diphenhydramine citrate tablets).

We also refer to your submissions dated June 27, 2005 and August 31, 2005.

Your June 27, 2005 submission, in addition to proposed SKU labeling, included shelf tray and gravity feed carton labels. Your August 31, 2005 submission contained revisions to the Drug Facts label and Principal Display Panel for the Advil PM Liqui-Gels (NDA 21-393) 32 count package size carton and blister back and the Advil PM Caplets (NDA 21-394) 20 count package size carton and bottle label in response to our June 14 and July 15, 2005 Supplement Request letters. According to your June 27, and August 31, 2005 submissions, the submitted labeling is representative of all SKUs for the respective NDA.

Our review of the Labeling section of your submission is complete, and we have identified the following recommendations and comments:

1. For applicable cartons with the following promotional statements:
  - a. Delete \_\_\_\_\_ in all labeling, where applicable.
  - b. Revise the statement "Helps you to get to sleep \_\_\_\_\_" to read "Helps you fall asleep and stay asleep \_\_\_\_\_"
  - c. Delete \_\_\_\_\_ statement.
  - d. Revise the phrase " \_\_\_\_\_" to "Sample - Not for Sale".

2. *Drug Facts Panel (Carton)*:
  - a. Revise the *Drug Facts Panel* (Booklet and Carton) according to the attached prototype label template:
    - i. The attached template is based on the Advil Liqui-Gel application (NDA 21-393) only.
    - ii. For the Advil PM Caplet (NDA 21-394) application, changes should be made by you, where applicable.
    - iii. Follow this Drug Facts template **in content only**. The font sizes for title, headings, subheadings, condensed text and other graphic features must be in accordance with 21 CFR 201.66.
  - b. Include under the “*Questions or comments*” section, the days of the week and times of the day when someone is available to respond to questions.
  - c. We reserve comment on the “cardioprotection warning” bulleted statement under the “**Ask a doctor or pharmacist before use if you are**” section until an agreement has been reached between you and the agency.
3. We remind you to delete the “NEW” flag from the Principal Display Panel after 6 months of OTC marketing.

This labeling review is preliminary based on the representative labeling in your August 31, 2005 submission plus additional comments that may apply to the submission dated June 27, 2005. We assume that the labeling for other package count sizes will be modeled after the submitted representative set for each NDA, respectively.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of labeling issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call me at 301-796-0869.

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

A

3 Page(s) Withheld

     § 552(b)(4) Trade Secret / Confidential

     § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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/s/

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Leah Christl

12/12/2005 03:26:49 PM

Division of OTC Drug Products Labeling Review

NDA 21-393 (Liqui-gels)  
NDA 21-394 (Caplets)

Submission Dates: June 27, 2005  
August 31, 2005  
Review Date: November 3, 2005

**Applicant's Representative:** Sharon C. Heddish  
Vice President, Worldwide Regulatory Affairs  
Wyeth Consumer Healthcare  
Five Giralda Farms  
Madison, NJ 07940  
973-660-5753

**Drug:** Advil® PM Liquigels/Coated Capsules  
(NDA 21-393: Solubilized Ibuprofen 200 mg  
/Diphenhydramine hydrochloride 25 mg Liquid  
Filled Capsules)  
(NDA 21-394 – Ibuprofen 200mg/Diphenhydramine  
citrate 38 mg (Caplets))

**Pharmacologic Category:** analgesic/nighttime sleep-aid

**Submitted:** Representative labeling for:  
NDA 21-393: 32 counts  
NDA 21-394: 20 counts

**Background:** On June 27, 2005 the sponsor resubmitted this application in response to a December 18, 2003 approvable letter in which the sponsor was informed that the data from the clinical studies did not adequately support the efficacy of this product for the the endpoint of sleep duration. On June 14, 2005 and July 15, 2005, the Agency sent IR letters to all OTC NSAID, NDA sponsors requesting labeling revision. On August 31, 2005, the sponsor submitted one representative set of labeling including the Agency's requested changes in the IR letters. This review is mainly based on the August 31 submission but also reviews the labeling submitted in the original resubmissions, where applicable.

**Reviewer's comments:** Strikethrough for deletion; redline for addition for labeling in general followed by specific recommendations for labels on each of the packages.

A. Carton Label: (NDA 21-393: 32s)  
(NDA 21-394: 20\*s)

\*a booklet attached to the back panel which will include the full Drug Facts label. The booklet is designed to be opened and resealed numerous times.

I. Principal Display Panel

(i) NEW!

~~Reviewer's comment~~: *The word can remain on the label for 6 months from date first marketed*

Advil® PM

(21-393 only):

LIQUI-GELS®

Solubilized Ibuprofen 200 mg, /Diphenhydramine HCl, 25 mg  
Pain Reliever (NSAID)/ Nighttime Sleep-Aid

Qty. Liqui-Gels®

(Liquid Filled Capsules)

(image of Liqui-Gel)

(on banner) Liquid Filled Capsules

II. Drug Facts (This is based on the Liqui-Gel application only. For the Caplet application, changes should be made by the sponsor, where applicable)

a. labeling

READ AND KEEP CARTON  
FOR COMPLETE WARNINGS  
AND INFORMATION

---

***Drug Facts***

***Active ingredients (in each capsule)***

***Purpose***

Diphenhydramine hydrochloride 25 mg .....	Nighttime sleep-aid
Solubilized ibuprofen equal to 200 mg ibuprofen (NSAID)* .....	Pain reliever

(present as the free acid and potassium salt)

\*nonsteroidal anti-inflammatory drug

---

*Uses*

- for relief of occasional sleeplessness when associated with minor aches and pains

*Reviewer's comment*

- helps you fall asleep and

*stay asleep*

*Reviewer's comment* The statement is a more consumer friendly language.

---

**Warnings**

**Allergy alert:** Ibuprofen may cause a severe allergic reaction especially in people allergic to aspirin. Symptoms may include:

- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop use seek medical help right away.

**Stomach bleeding warning:** This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID (aspirin, ibuprofen, naproxen or others)
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

---

**Do not use**

- if you have ever had an allergic reaction to any other pain reliever/fever reducer

*Reviewer's comment* The statement is inappropriate.

- in children under 12 years of age
- right before or after heart surgery
- with any other product containing diphenhydramine, even one used on skin
- if you have sleeplessness without pain

*Reviewer's comment* The statement helps to differentiate between sleeplessness with and without pain.

---

**Ask a doctor before use if you have**

- a breathing problem such as emphysema or chronic bronchitis
- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach or stomach pain
- ulcers
- bleeding problems
- high blood pressure
- heart or kidney disease
- taken a diuretic
- reached age 60 or older
- glaucoma
- trouble urinating due to an enlarged prostate gland

---

**Ask a doctor or pharmacist before use if you are**

- taking sedatives or tranquilizers, or any other sleep-aid
- taking any other drug containing an NSAID (prescription or nonprescription)
- under a doctor's care for any ~~continuing medical~~

~~illness~~

~~Reviewer's comment:~~ *This statement was made consistent with the nighttime sleep-aid monograph language. It makes the stricken language from the updated NSAID template redundant. Gave priority to the monograph language over the NSAID labeling template.*

- taking any other antihistamines
- taking a blood thinning (anticoagulant) or steroid drug
- TBD

~~Reviewer's comment:~~ *Sponsor included TBD (to be determined) pending the outcome of the statement " \_\_\_\_\_ requested in its June 27, 2005 labeling supplement. This statement is still under review by the agency. We should reserve comment on this until after a future Regulatory Briefing and pending responses to other NDAs containing this statement.*

- taking any other drug

~~Reviewer's comment:~~ *This statement was added per the NSAID labeling template. Other specific types of drugs in other included statements seem to make this statement unnecessary, but it's*

*better to leave it in, in case other drugs not cited in the other statements could cause an adverse reaction.*

---

**When using this product**

- drowsiness will occur
  - avoid alcoholic drinks
  - do not drive a motor vehicle or operate machinery
  - take with food or milk if stomach upset occurs
  - long term continuous use may increase the risk of heart attack or stroke
- 

**Stop use and ask a doctor if**

- you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding.
- pain gets worse or lasts more than 10 days
- sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness.

*Reviewer's comment: The change in word is consistent with nighttime sleep-aid monograph language.*

- stomach pain or upset gets worse or lasts
  - redness or swelling is present in the painful area
  - any new symptoms appear
- 

**If pregnant or breast-feeding**, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

**Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

---

**Directions**

- do not use take more than directed

*Reviewer's comment: The substituted word is more accurate for oral ingestion.*

- do not take longer than 10 days unless directed by a doctor (see Warnings)

*Reviewer's comment: The additions came from the updated NSAID labeling template*

- adults and children 12 years and over: take 2 capsules at bedtime. →

*Reviewer's comment:* The addition was for consistency with other nighttime sleep aid labeling (e.g., Unisom), and clarity. Stricken words are not supported by data.

- do not take more than 2 capsules in 24 hours.

*Reviewer's comment:* Stricken words are not supported by data.

---

**Other information**

- each capsule contains: potassium 15 mg
  - read all warnings and directions before use. Keep carton.
  - store at 20-25°C (68-77°F)
  - avoid excessive heat 40°C (above 104°F)
  - protect from light
- 

**Inactive ingredients**

D&C red no. 33, FD&C blue no. 1, fractionated coconut oil, gelatin, lecithin, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan, sorbitol

---

Questions or comments? Call 1-800-88-ADVIL

*Reviewer's comment:* We encourage inclusion of days of week and times when someone is available to answer the telephone.

---

- b. The font and graphic specifications for "Drug Facts" labeling are in accordance with 21 CFR 201.66.

III. Side Panels (Left/Right depending on carton size)

NEW!

*Reviewer's comment:* The word can remain on the label for 6 months from the date first marketed

Advil® PM

*Reviewer's comment:* Data not shown to support stricken words.  
Applicant's claim of

Wyeth®

Product inside sealed in plastic blister with foil backing  
Do Not Use if plastic blister or foil barrier is broken.

(enclosed in a box)

Visit us at [www.advil.com](http://www.advil.com)  
Dist. By Wyeth Consumer Healthcare, Madison, NJ 07940, Made in USA  
U.S. Patent Nos. 5,071,643 and 5,360,615  
By arrangement with R.P. Scherer Corp.  
Liqui-Gels<sup>®</sup> is a trademark of R.P. Scherer Corp

UPC Code  
Lot No            Exp.

B. Gravity feed dispenser label for 4-count size (submitted on June 27, 2005)

I. PDP

*Reviewer's comment:* We are only commenting on the promotional statements. It is assumed that it will be revised to be the same as submitted in the representative label date August 31, 2005.

Helps you fall asleep and ~~stay~~ stay asleep

*Reviewer's comment:* See comments under "Uses" section.

*Reviewer's comment:* Data were not shown to substantiate the stricken words. Applicant's claim of

*Reviewer's comment:*

D. Booklet

Drug Facts for trial size to be attached to the back panel of the applicable cartons.

**[REDACTED]** *Comments are the same as Drug Facts for Carton label above*

RECOMMENDATIONS:

I. Inform the sponsor that this labeling review is preliminary based on its August 31, 2005 submission of a new representative set of labeling. Labeling for other packages should be modeled after the submitted representative set. Thus, comments were based on this set, plus additional comments that might not apply to the original submitted labeling. The following labeling revisions can be related to the sponsor. Request the sponsor to resubmit all revised labeling (all SKUs and sample) for our review and comment, prior to an action letter as follows:

1. Drug Facts (Booklet and cartons based on the Liqui-gel formulation. The sponsor needs to change accordingly for the Caplet formulation, where applicable)

Revise according to the attached prototype template labeling. (Note: The template does not contain the TBD "cardioprotective" statement)

2. For applicable cartons with the following promotional statements

- a. Delete \_\_\_\_\_ in all labeling, where applicable.

- b. Revise the statement "Helps you get to sleep \_\_\_\_\_" to "Helps you fall asleep and stay asleep"

- c. Delete " \_\_\_\_\_ statement.

- d. Revise the phrase " \_\_\_\_\_" to "Sample – Not for Sale"

3. Recommend to the sponsor to include under the "Drug Facts" label "Questions or comments" section, the days of the week and times of the day when someone is available to respond to questions.

II. Inform the sponsor to delete the flag "NEW" once the product has been marketed for 6 months.

III. Please include the attached prototype when communicating with the sponsor regarding the labeling revisions. Also, the template does not contain the Ibuprofen/Aspirin Cardioprotective statement. If the statement is available at the time of communication, please include such statement, otherwise notify the sponsor that this statement will be related at a later date.

---

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

---

Marina Chang, R. Ph.  
Leader, Team I Concurrence

Attachment: Drug Facts labeling prototype

B

3 Page(s) Withheld

   § 552(b)(4) Trade Secret / Confidential

   § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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/s/

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Michael Benson  
11/4/2005 02:02:06 PM  
INTERDISCIPLINARY

Marina Chang  
11/4/2005 02:07:41 PM  
INTERDISCIPLINARY



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-393

**DISCIPLINE REVIEW LETTER**

Wyeth Consumer Healthcare  
Attention: Mary Davis  
Director, Regulatory Affairs  
5 Giralda Farms  
Madison, NJ 07940

Dear Ms. Davis:

Please refer to your October 16, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil PM Liqui-Gels (200 mg ibuprofen/25 mg diphenhydramine HCl capsules).

We also refer to your submission dated June 27, 2005.

Our review of the Biopharmaceutics section of your submission is complete, and we have identified the following deficiencies:

We recommend that you incorporate the following as the final dissolution method and specification into the manufacturing control and stability program of the test product Advil PM Liqui-Gels:

- Method: Apparatus USP I (Basket) in 900 ml phosphate buffer, 200 mM, pH 7.2, rotational speed 100 rpm
- Specification:  $Q = \frac{m}{M}$  at 30 minutes for both active components - ibuprofen and diphenhydramine HCl

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call me at 301-796-0869.

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**

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/s/

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Leah Christl

10/18/2005 04:44:49 PM

4615105



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-393  
NDA 21-394

**INFORMATION REQUEST LETTER**

Wyeth Consumer Healthcare  
Attention: Sharon C. Heddish  
Vice President, Global Regulatory Affairs  
Five Giralda Farms  
Madison, NJ 07940

Dear Ms. Heddish:

Please refer to your October 16, 2001 new drug applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil PM Liqui-Gels (200 mg ibuprofen/25 mg diphenhydramine HCl capsules) and Advil PM Caplets (200 mg ibuprofen/38 mg diphenhydramine HCl tablets).

We also refer to your submissions dated June 27, 2005.

We are reviewing the Clinical 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.

In Table 2 in the ISS report in the June 27, 2005 submission, only the overall distribution of subjects was included. Submit an expanded table listing all the studies that contributed any safety data to these applications. Provide the following information in the table:

- a. individual study (reference) number
- b. a brief description of study type and design
- c. the number of patients exposed by:
  - i. treatment type
  - ii. dose
  - iii. duration of treatment

Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

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

NDA 21-393; NDA 21-394

Page 2

If your submission only contains paper, send it to the following address:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Office of Nonprescription Products, HFD-560  
Attention: Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Nonprescription Products, HFD-560  
Attention: Document Room  
9201 Corporate Blvd.  
Rockville, Maryland 20850

If you have any questions, call me at 301-827-2248.

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

7/15/05



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-393  
NDA 21-394

Wyeth Consumer Healthcare  
Attention: Sharon C. Heddish  
Vice President, Global Regulatory Affairs  
Five Giralda Farms  
Madison, NJ 07940

Dear Ms. Heddish:

We acknowledge receipt on June 27, 2005 of your June 27, 2005 resubmissions to your new drug applications for Advil PM Liqui-Gels (200 mg ibuprofen/25 mg diphenhydramine HCl capsules) and Advil PM Caplets (200 mg ibuprofen/38 mg diphenhydramine HCl tablets).

We consider this a complete, class 2 response to our December 18, 2003 action letter. Therefore, the user fee goal date is December 27, 2005.

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 reference the waiver granted on October 11, 2001 for the pediatric study requirement for the age range of birth to less than 12 years of age for these applications.

If you have any question, call me at (301) 827-2248.

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration <b>CERTIFICATION: FINANCIAL INTERESTS AND          ARRANGEMENTS OF CLINICAL INVESTIGATORS</b>	Form Approved: OMB No. 0910-0396 Expiration Date: February 28, 2006.
--	---

*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.*

7

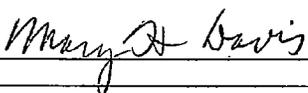
- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected 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		

- (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)).

L

- (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 Mary H. Davis	TITLE Director, Regulatory Affairs
FIRM / ORGANIZATION Wyeth Consumer Healthcare, 5 Giralda Farms, Madison, NJ 07940	
SIGNATURE 	DATE 4/29/05

**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  
 5600 Fishers Lane, Room 14C-03  
 Rockville, MD 20857

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Applicant Information		
NDA <b>21-393</b>	Efficacy Supplement Type <b>SE-</b>	Supplement Number
Drug: <b>ibuprofen 200 mg / diphenhydramine HCl 25 mg</b>		Applicant: <b>Wyeth Consumer Healthcare (formerly Whitehall-Robins Healthcare)</b>
RPM: <b>Jane A. Dean, RN, MSN</b>		HFD- <b>550</b> Phone # <b>301-827-2536</b>
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): <b>NA</b>
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		<b>4 (New Combination)</b>
• Other (e.g., orphan, OTC)		<b>OTC</b>
❖ User Fee Goal Dates		<b>3 January 2004</b>
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>Exclusivity summary</li> </ul>	NA
<ul style="list-style-type: none"> <li>Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!</i></li> </ul>	( ) Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	NA
<b>General Information</b>	
❖ Actions	
<ul style="list-style-type: none"> <li>Proposed action</li> </ul>	( ) AP ( ) TA (X) AE ( ) NA
<ul style="list-style-type: none"> <li>Previous actions (specify type and date for each action taken)</li> </ul>	<b>APPROVABLE 8 August 2002</b>
<ul style="list-style-type: none"> <li>Status of advertising (approvals only)</li> </ul>	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> <li>Press Office notified of action (approval only)</li> </ul>	( ) Yes (X) Not applicable
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> <li>Division's proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	NA
<ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>	NA
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	NA
<ul style="list-style-type: none"> <li>Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)</li> </ul>	NA
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	NA
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> <li>Division proposed (only if generated after latest applicant submission)</li> </ul>	NA
<ul style="list-style-type: none"> <li>Applicant proposed</li> </ul>	NA
<ul style="list-style-type: none"> <li>Reviews</li> </ul>	NA
❖ Post-marketing commitments	
<ul style="list-style-type: none"> <li>Agency request for post-marketing commitments</li> </ul>	NA
<ul style="list-style-type: none"> <li>Documentation of discussions and/or agreements relating to post-marketing commitments</li> </ul>	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>EOP2 meeting (indicate date)</li> </ul>	NA
<ul style="list-style-type: none"> <li>Pre-NDA meeting (indicate date)</li> </ul>	NA
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (indicate date; approvals only)</li> </ul>	NA
<ul style="list-style-type: none"> <li>Other</li> </ul>	NA

Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	<b>Office Director Memorandum 19 December 2003</b>
<b>Clinical Information</b>	
❖ Clinical review(s) (indicate date for each review)	<b>12 December 2003</b>
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	NA
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	NA
❖ Demographic Worksheet (NME approvals only)	NA
❖ Statistical review(s) (indicate date for each review)	<b>4 November 2003</b>
❖ Biopharmaceutical review(s) (indicate date for each review)	<b>28 August 2003</b>
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	NA
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	<b>21 November 2003</b>
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	NA
• Review & FONSI (indicate date of review)	NA
• Review & Environmental Impact Statement (indicate date of each review)	NA
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	NA
❖ Facilities inspection (provide EER report)	Date completed: NA ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	NA
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NA
❖ CAC/ECAC report	NA

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/s/

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Jane Dean

12/30/03 11:59:44 AM

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**

Center for Drug Evaluation and Research, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20857

**To:** Ms. Mary Davis

**From:** Ms. Jane A. Dean, RN, MSN

**Fax:** 973-660-7187

**Fax:** 301-827-2531

**Phone:** 973-660-5825

**Phone:** 301-827-2090

**Pages:** 1 (including cover page)

**Date:** November 19, 2003

**Re:** NDA 21-393 CMC comments

**Urgent**    **For Review**    **Please Comment**    **Please Reply**    **Please Recycle**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

**Comments:** Dear Mary, the Division wishes to convey the following request relating to CMC issues:

- The limit for unspecified individual degradant related to diphenhydramine as NMT based on ICH threshold for qualification is not acceptable. The limit should be established based on ICH threshold for identification, which for diphenhydramine related degradant is →. The limit of total unspecified degradants should be revised accordingly.

Please feel free to call me if you have any questions.

Sincerely,

Jane A. Dean  
Project Manager

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/s/

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Jane Dean  
11/19/03 10:33:39 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-393  
NDA 21-394

Wyeth Consumer Healthcare  
Attention: Ms. Sharon C. Heddish  
Vice President, Regulatory Affairs  
Five Giralda Farms  
Madison, NJ 07940-0871

Dear Ms. Heddish:

We acknowledge receipt on July 3, 2003 of your June 30, 2003 submission to your new drug application (NDA) for Advil PM Caplets and Advil PM Liquigels.

We consider this a complete, class 2 response to our August 8, 2002 action letter. Therefore, the user fee goal date is January 3, 2004.

If you have any question, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301)827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, RPh  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic and  
Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Carmen DeBellas  
8/5/03 04:23:10 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-393  
NDA 21-394

Wyeth Consumer Healthcare  
Attention: Sharon C. Heddish  
Vice President, Worldwide Regulatory Affairs  
Five Giralda Farms  
Madison, NJ 07940

Dear Ms. Heddish:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil PM (ibuprofen/diphenhydramine HCl/citrate).

We refer also to your April 23, 2003, request for formal dispute resolution received on April 24, 2003. The appeal concerned the August 8, 2002, approvable letter issued by the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products and the Division of Over-the-Counter Drug Products. Subsequent appeals of this decision were made to the Office of Drug Evaluation V and the Office of New Drugs, and were denied in decisions dated January 10, and February 26, 2003, respectively.

At your request, a meeting was held on May 20, 2003, to discuss your appeal (minutes attached). During that meeting, you presented new analyses of data from your clinical investigations that have not been reviewed by the review divisions. As further discussed by you, Dr. Roger Berlin, Dr. John Jenkins and Ms. Kim Colangelo on June 13, 2003, these new analyses should be submitted to your NDA as part of a complete response to the August 8, 2002 approvable letter. We commit to reviewing this response promptly and before the PDUFA due date.

If you have any questions, call Kim Colangelo, Formal Dispute Resolution Project Manager, at (301) 594-5479.

Sincerely,

*{See appended electronic signature page}*

Janet Woodcock, M.D.  
Director  
Center for Drug Evaluation and Research

**MEETING MINUTES  
FORMAL DISPUTE RESOLUTION**

**Date:** May 20, 2003

**Time:** 9:00 – 10:30 AM EDT

**Location:** WOC2, Conference Room “C”

**Application:** NDA 21-393 and 21-394

**Product:** Advil PM (ibuprofen/diphenhydramine)

**Sponsor:** Wyeth Consumer Healthcare

**Attendees:**

Center for Drug Evaluation and Research

Janet Woodcock, MD – Director

John Jenkins, MD – Director, Office of New Drugs

Jane Axelrad, JD – Associate Director for Policy

Robert Temple, MD – Director, Office of Medical Policy

Kim Colangelo – Formal Dispute Resolution Project Manager

Wyeth Consumer Healthcare

Roger Berlin - President, Global Scientific Affairs

Stephen Cooper - Sr. Vice President, Clinical and Medical Affairs

Geraldine Doyle – Sr. Director, Clinical and Medical Affairs

Sharon Heddish – Vice President, Global Regulatory Affairs

Joel Waksman – Assistant Vice President, Biostatistics and Data Management

Geoff Levitt- Vice President and Chief Regulatory Counsel

Douglas Rogers - President, Wyeth Consumer Healthcare U.S.

Nancy Buc – Partner, Buc and Beardsley (Outside Counsel)

**Background:**

Wyeth Consumer Healthcare (“Wyeth”) submitted a request for formal dispute resolution regarding their applications for Advil PM (ibuprofen/diphenhydramine HCl/citrate), NDA 21-393 and 21-394. Specifically, they are appealing the August 8, 2002, approvable decision by the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products and Division of Over-the-Counter Drug Products. This decision was discussed with the reviewing divisions on September 12, 2002. The first iteration of formal dispute resolution was submitted December 10, 2002, to Dr. Jonca Bull, Director, Office of Drug Evaluation V, and was denied on January 10, 2003. A second iteration of the appeal was submitted February 5, 2003, to Dr. Jenkins. This appeal was also denied in a letter dated February 26, 2003. This is the third iteration of this appeal, submitted to Dr. Woodcock on April 23, 2003. Wyeth requested a meeting with Dr. Woodcock to discuss their appeal.

**Discussion:**

Wyeth opened the meeting with a brief presentation of information (slides attached).

Three endpoints were assessed in the clinical trials: pain, sleep latency and sleep duration. Trial designs utilized a modified dental pain model (post-operative patients) comparing the combination (ibuprofen/diphenhydramine) to placebo. To assess pain, patients were awakened at 90 and 120 minutes. Two pivotal studies (98-01 and 98-02) were designed with sleep latency as a primary endpoint, and sleep duration as a secondary endpoint. The primary endpoint for Study 98-02 was later changed to sleep duration following analysis of the results from Study 98-01, which showed that the combination did not show a statistically significant difference in sleep latency as compared to ibuprofen alone.

Wyeth noted that, based on pharmacokinetic parameters, ibuprofen (with a shorter half-life) would be expected to have a quicker onset of action, while diphenhydramine (with a longer half-life) would have a slower onset.

Therefore Wyeth speculated that the effect of diphenhydramine on the early endpoint (sleep latency) could be “masked” by the effect of the ibuprofen.

Wyeth displayed results of analyses performed to address questions raised in Dr. Jenkins’ response to the second iteration of the request for formal dispute resolution.

One such question was the effect of the awakenings on the assessment of sleep duration. Wyeth performed an analysis to determine the number of patients who were asleep at 150 minutes (following awakenings at 90 and 120 minutes). Over 89% of the patients were back to sleep at 150 minutes. A subset analysis of those who were asleep at 150 minutes showed similar effects in magnitude of sleep duration as compared to the entire cohort. Therefore, Wyeth concluded that the awakenings did not impact the duration of sleep.

Another issue raised by Dr. Jenkins was the use of a categorical scale to measure sleep duration. Wyeth addressed concerns raised about the robustness of the scale, and the broadness of the lowest category (less than 5 hours). Analyses performed by Wyeth suggest that it would be *more* difficult to achieve statistical significance using the categorical scale instead of a continuous scale, therefore making it more robust.

Finally, Wyeth provided two analyses to support the use of the “broad” lowest category in the sleep duration categorical scale. The first, using data from Study 98-02, showed data on the time to rescue (or cessation of effect) based on when patients asked for additional relief (e.g., additional medication). Another analysis was done which arbitrarily assigned negative values to the lowest category yet still showed statistically significant results in sleep duration for the combination as compared to ibuprofen alone.

Attendees at the meeting agreed that ibuprofen is effective for pain, but CDER attendees questioned the additional benefit provided by the combination product. Wyeth believes that the actual use study (which did not include awakenings) supports the effectiveness of the combination (results were similar to the controlled studies).

Wyeth stated that they would be open to discussing revisions to the proposed indication for Advil PM.

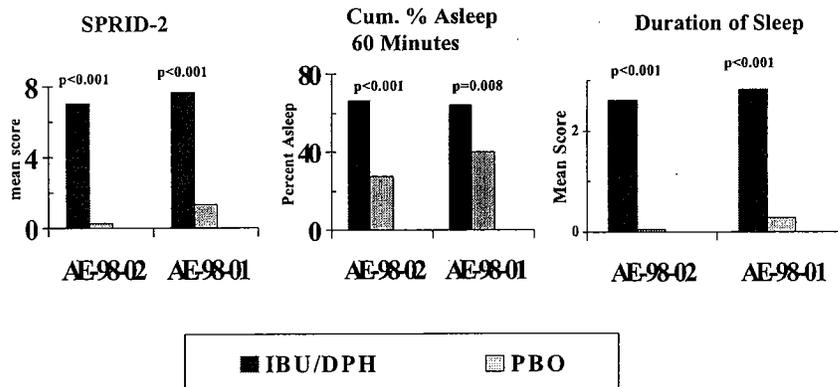
**Action Item:**

Wyeth will submit the new analyses (including supporting data) presented at the meeting today to the review division (Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products). Wyeth agreed to have those data to the division within one work week. Following submission of the data, a timetable for review and further discussions with Wyeth will be determined.

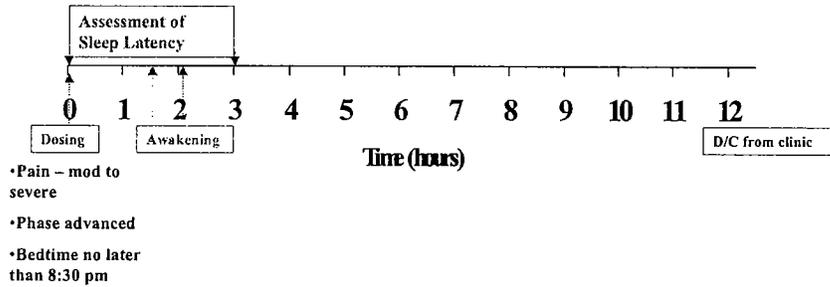
## Ibuprofen/Diphenhydramine Proposed Indications

- For the relief of occasional sleeplessness when associated with minor aches and pains
- Helps you to get to sleep

### Advil PM vs Placebo Studies AE-98-02 and 01



## Study Design Flow Chart

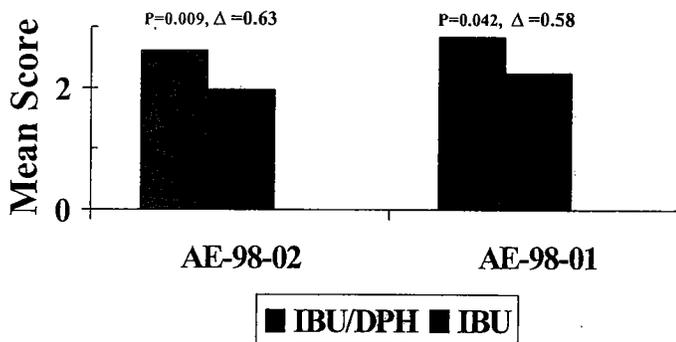


Assessment of Sleep Duration

<5 h	5-6 h	6-7 h	7-8 h	8-9 h	> 9 h
0	1	2	3	4	5

3

### IBU/DPH vs IBU Duration of Sleep



4

## Subjects Awakened at 120 min, and then Asleep at 150 min

	Awakened at 120 minutes	Sleep resumed at 150 minutes (%*)
<b>AE-98-02</b>		
<b>IBU-DPH (n=119)</b>	<b>95</b>	<b>87 (92%)</b>
<b>IBU (n=123)</b>	<b>72</b>	<b>64 (89%)</b>
<b>AE-98-01</b>		
<b>IBU-DPH (n=122)</b>	<b>61</b>	<b>57 (93%)</b>
<b>IBU (n=118)</b>	<b>54</b>	<b>48 (89%)</b>

\*Based on those who were awakened at 120 minutes

5

## Duration of Sleep for Subjects Asleep at 150 min

	Sample Size Asleep at 150 min	Mean Duration of Sleep*	Δ p-value
<b>AE-98-02</b>			
<b>IBU-DPH (n=119)</b>	<b>97</b>	<b>2.96</b>	<b>Δ = 0.59</b>
<b>IBU (n=123)</b>	<b>78</b>	<b>2.37</b>	<b>p = 0.03</b>
<b>AE-98-01</b>			
<b>IBU-DPH (n=122)</b>	<b>76</b>	<b>3.62</b>	<b>Δ = 0.65</b>
<b>IBU (n=118)</b>	<b>67</b>	<b>2.97</b>	<b>p = 0.03</b>

\*Reported by category

(0=<5 hrs, 1=5-6 hrs, 2=>6-7 hrs, 3=>7-8 hrs, 4=>8-9 hrs, 5=>9 hrs)

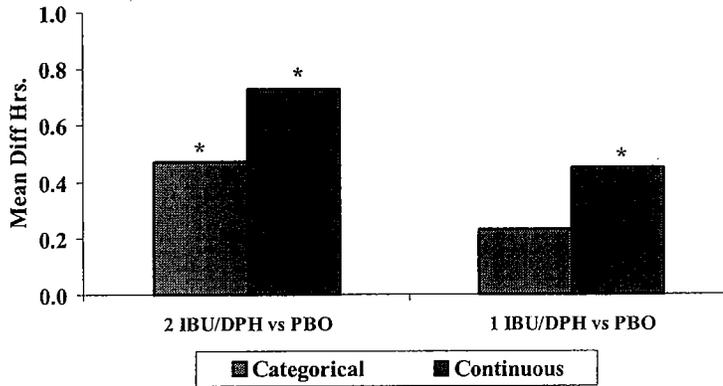
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### Categorical Scale for Sleep Duration

<5 hrs	5-6 hrs	6-7 hrs	7-8 hrs	8-9 hrs	> 9 hrs
0	1	2	3	4	5

7

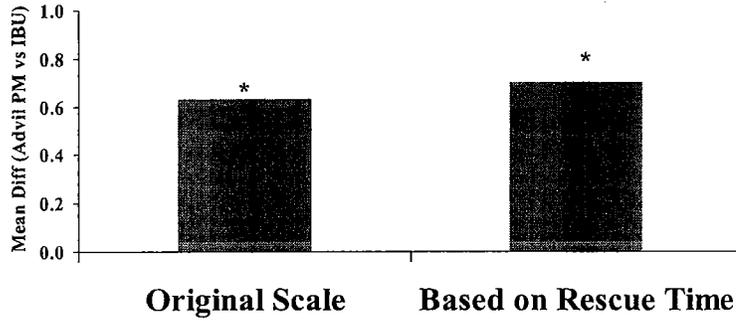
### Categorical vs Continuous Measures of Duration AE-97-08



\* p < 0.05 vs PBO

8

**IBU/DPH vs IBU Treatment Differences  
Duration of Sleep – AE-98-02**



\* p <0.05 vs IBU

9

**Methodology for Recategorization of <5 hour Sleep Duration Data**

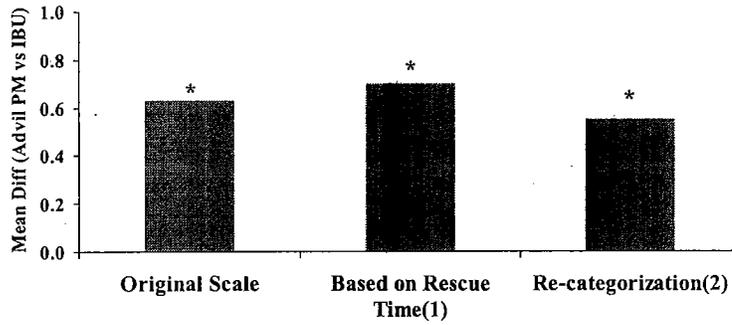
	Study AE-98-02	
	Combo (n=119)	IBU (n=123)
# whose duration was <5 hrs	26	41
# (%) reclassified as “less sleep” (i.e., -1)	20 (75%)	10 (25%)
# (%) reclassified as “more sleep” (i.e., 0)	6 (25%)	31 (75%)

Originally assessed with 6 pt categorical scale:  
0 = <5 hrs, 1=5-6 hrs, 2=>6-7 hrs, 3=>7-8 hrs, 4=>8-9 hrs, 5=>9 hrs

Recategorized using a 7 pt scale:  
-1 = <5 hr (-), 0=<5 hrs (+), 1= 5-6 hrs, 2=>6-7 hrs, 3=>7-8 hrs, 4=>8-9 hrs, 5=>9 hrs

10

**IBU/DPH vs IBU Treatment Differences  
Duration of Sleep – AE-98-02**



\* p < 0.05 vs IBU

(1): <5 hr category divided into hourly sub-categories based on rescue time-sleep latency

(2): 75% of IBU subjects in <5 hr category re-assigned to "more sleep" (< 5 hrs (+)), and 75% of IBU/DPH to "less sleep" (< 5 hrs (-)).

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/s/

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Janet Woodcock  
6/16/03 05:50:07 PM



NDA 21-393  
NDA 21-394

Wyeth Consumer Healthcare  
Attention: Sharon C. Heddish  
Vice-President, Worldwide Regulatory Affairs  
5 Giralda Farms  
Madison, NJ 07940

Dear Ms. Heddish:

We refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil® PM Liquigels and Advil® PM Caplets (hereinafter referred to as Advil PM). Your formal dispute resolution request (FDRR) dated February 5, 2003, received February 6, 2003, concerns the August 8, 2002, approvable letter issued by the Division of Over-the-Counter Drug Products and the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and the January 10, 2003, response to your December 10, 2002, FDRR to the Director of the Office of Drug Evaluation V, in which the approvable action was upheld.

In your FDRR dated February 5, 2003, you disagree with the decision communicated in the approvable letter and the response to the first FDRR that the applications could not be approved since the contribution of diphenhydramine (DPH) in the proposed combination product has not been established. You specifically argue that adequate data have been provided in two studies (98-01 and 98-02) to demonstrate that DPH contributes to the claimed effects of the proposed combination by statistically significantly extending the duration of sleep compared to the single ingredient ibuprofen alone. You state your belief that such a demonstration of an effect of DPH on sleep duration in conjunction with the effect of ibuprofen on pain and sleep latency meets the standards under the combination policy for OTC drugs (21 CFR 330.10(a)(4)(iv)) and that the applications should be approved for “\_\_\_\_\_”. You also argue that it is not necessary to show that DPH has an effect on more than one sleep endpoint (e.g., on sleep latency as well as sleep duration) in order to demonstrate its contribution to the claimed effects of the proposed combination. Specifically, you argue that it is not necessary that DPH be shown to have an effect on sleep latency since an effect on sleep latency has already been demonstrated for the ibuprofen component of the combination in the proposed patient population and that, therefore, demonstration of an effect of DPH on sleep duration is sufficient for approval.

A review of the administrative record for this application shows that there have been multiple meetings and discussions between the Agency and Wyeth Consumer Healthcare (WCH) throughout the development program for Advil PM. The record shows that the Agency clearly informed WCH that the combination policy would be applicable to this new fixed-dose

combination of ibuprofen and DPH. Specifically, the Agency informed WCH that it would be necessary to demonstrate an effect of each component to the claimed effects of the proposed combination product in adequate and well-controlled clinical trials in the target population.<sup>1</sup> The design of the clinical program for Advil PM demonstrates that WCH clearly understood this requirement and WCH does not dispute the need to demonstrate the contribution of the individual components in the FDRR. Therefore, the applicability of the Agency's regulatory policy with regard to fixed-dose combinations is not in dispute. What is in dispute is whether the data WCH submitted in the Advil PM NDA adequately meet this regulatory standard for approval.

WCH's clinical development program for Advil PM included three clinical trials (97-01, 98-01, and 98-02) that included the appropriate full or partial factorial design necessary to evaluate the contribution of one (98-01 and 98-02) or both (97-01) of the individual ingredients to the claimed effects of the proposed combination product.<sup>2</sup> These three studies were all conducted in a population of patients with pain following dental surgery. WCH also conducted three additional clinical trials that were designed to evaluate other important scientific and regulatory questions for Advil PM. These studies included a dose response study, an evaluation of the efficacy and safety of Advil PM in patients with a different type of pain (tension headache) and sleeplessness, and a safety study to evaluate the safety of nightly use of Advil PM for 10 days. A summary of my review of these six clinical studies is included in Attachment 1.

WCH notes in the FDRR that "the key remaining question is whether each of the two ingredients has been shown to make a contribution to the claimed effects." I agree that this is the primary issue in dispute. In the approvable letter the divisions concluded that "the benefit of diphenhydramine in the combination product has not been established" and directed WCH to "conduct another study evaluating sleep duration and sleep latency using methodology that will not bias the outcome of either endpoint." The divisions further indicated that the "data from this study should also establish a consistent result between the sleep endpoints. If you are able to conduct a single study that adequately establishes the benefit of the individual components to the combination product, the clinical information in the current application would suffice as supportive data." In the FDRR, WCH disagrees with the conclusion that the benefit of DPH in the combination has not been established, arguing instead that the data demonstrate a statistically and clinically significant effect of DPH on sleep duration in studies 98-02 and 98-01 (the latter of which WCH characterizes as supportive). WCH also interprets the divisions' expectation for consistency with regard to the sleep endpoints as a requirement that they must show that DPH has an effect on both sleep latency and sleep duration in order to gain approval. I will analyze each of these issues separately.

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<sup>1</sup> The Agency has not previously approved a new drug application for a fixed-dose combination of an OTC analgesic and a sleep aid for the

<sup>2</sup> The partial factorial design utilized in Studies 98-01 and 98-02 is acceptable since the primary goal of these studies was to demonstrate an effect of DPH in the combination over ibuprofen. Inclusion of a DPH only arm was not necessary since there was no expectation that DPH alone would have an effect on pain either alone or in the combination. This was strongly supported by the results of study 97-01, which included a full factorial design.

Demonstration of a contribution of DPH to the claimed effects of the combination

It is clear from reviewing the administrative record of this application that the Agency considered Advil PM to be a significant new combination of active ingredients for an indication that had not previously been granted to an OTC product; i.e.,

It is also clear that the Agency expected the sponsor to demonstrate the safety and efficacy of this new combination, including the contribution of the individual active ingredients, in adequate and well-controlled trials in a population of patients that could reasonably be expected to benefit from the fixed-dose combination. There were a number of discussions between the Agency and WCH regarding the design of the clinical study program to accomplish these goals. WCH has not challenged in the FDRR the need to meet the combination policy and it is clear from the scope of the development program for Advil PM that WCH understood approval would require a showing of substantial evidence of safety and effectiveness of the new combination as required under the statute. This is exemplified by the number and types of clinical trials included in WCH's clinical development program.

It is also clear from the administrative record and the design of the individual clinical trials that WCH's primary hypothesis regarding addition of DPH was that its primary contribution to the claimed effects of the combination was that it would have an effect on sleep latency. Sleep latency was the primary pre-specified sleep efficacy endpoint for studies 97-01, 98-01, 98-02, 98-03, and 98-04. It was only after WCH had failed to demonstrate an effect of DPH on sleep latency in other studies, including study 98-01, that a decision was made to elevate sleep duration, one of several pre-specified secondary sleep endpoints in each of these studies, to be a second primary endpoint in study 98-02. In essence, the clinical development program clearly demonstrated that WCH's primary hypothesis about the effects of DPH in the combination on sleep in this patient population was incorrect since no statistically or clinically significant effect on sleep latency was demonstrated.

Sleep duration was one of at least five pre-specified secondary sleep endpoints in studies 97-01, 98-01, and 98-02. While the design of the phase 3 pivotal studies was adequate for assessment of sleep latency and pain, it was significantly flawed with regard to assessment of sleep duration. An important flaw was the waking of patients at specified intervals during the first 2-3 hours after administration of study drug in order to assess pain. These forced awakenings could have altered the sleep pattern that would otherwise have been observed in patients had the awakenings not occurred and could have induced an artificial benefit that would not have been seen in un-awakened patients. For example, the pharmacokinetic profile for DPH reported by WCH in the FDRR demonstrates that on average the blood levels of DPH exceed the "minimum effective concentration" of DPH after approximately 90 minutes and the C<sub>max</sub> occurs at approximately 4-5 hours.<sup>3</sup> In studies 98-01 and 98-02 the patients were awoken for pain assessments at 90 and 120 minutes, times at which the majority of patients would have been expected to have blood levels of DPH at or above the "minimum effective concentration." It is possible that the DPH in the combination allowed patients to return to sleep more rapidly than those patients who did not receive DPH; i.e., the ibuprofen and placebo treatment groups. This study design might,

<sup>3</sup> The pharmacokinetic data referenced here were provided by WCH in the FDRR. For the sake of the present discussion, I have accepted WCH's definition of the "minimum effective concentration" of DPH.

therefore, tend to favor showing an effect of DPH in the combination on sleep duration. This is directly relevant to the interpretation of the study data since the study design does not accurately mimic the actual use of the product by consumers where forced awakenings at specified intervals would not normally occur. In other words, the apparent benefit of DPH in the combination may be an artifact of the forced awakenings.

In addition to the problems with the study design, the methods utilized by WCH for collecting data on sleep duration and the methods for data analysis were flawed. The Agency would normally expect that patient-reported data on sleep duration would be captured as the number of hours (including partial hours) slept expressed and analyzed as a continuous variable. WCH chose instead to capture the data in arbitrary categories (e.g., <5 hours of sleep, 5 to 6 hours, 6+ to 7 hours). This transformation of continuous data into categories has the potential to result in data analyses that are not meaningful or interpretable. For example, under WCH's schema, a patient who reported 2 hours of sleep would be categorized and analyzed the same as a patient who reported 4.5 hours of sleep and a patient who reported 9 hours of sleep would be categorized and analyzed the same as a patient who reported 11 hours of sleep. The problems associated with such a categorical analysis of a continuous variable were demonstrated by study 97-08 (see Attachment 1). In that study patients were asked to report the number of hours slept after the first dose of study drug. When the data were analyzed as a continuous variable, statistically significant differences were observed between all active treatment groups and placebo (e.g., higher dose Advil PM, lower dose Advil PM, and Tylenol PM). When the same data were analyzed using the categorical methods WCH used in the other studies, only the higher dose of Advil PM was statistically significantly better than placebo.

This demonstration that the statistical conclusions derived from a study of sleep duration are highly dependent on the analysis methodology used is important to the interpretation of the results of the analysis of sleep duration reported by WCH for studies 97-01, 98-01, and 98-02. In these studies, a significant percentage of the patients reported either less than 5 hours or greater than 9 hours of sleep, and much of the observed benefit of the combination over ibuprofen was seen in these groups. It is possible that the statistically significant superiority of the combination over ibuprofen reported by WCH based on the categorical analysis of sleep duration would not have been observed had the data been collected and analyzed as a continuous variable, as the Agency would expect for a study primarily designed to assess sleep duration.

It could be argued that the Agency should have been aware of the flaws in the study design and analysis plans with regard to sleep duration and should have warned WCH of the potential consequences before the studies were initiated. I do not believe such an argument has merit. First, the primary responsibility for the design of adequate and well-controlled studies rests with the sponsor, not the Agency. Second, at the time the study protocols were submitted to the Agency, sleep duration was one of several secondary sleep endpoints. While the study design and analysis plan included serious flaws with regard to the analysis and interpretation of data for sleep duration, the study design and analysis plan were appropriate for evaluation of sleep latency, the pre-specified primary endpoint. The flaws noted above in the study design and analysis plan only became critical when WCH decided to elevate sleep duration to be a second primary endpoint in study 98-02 after the study had already been completed. Had the sponsor

demonstrated an effect of DPH in the combination on sleep latency, the pre-specified primary sleep endpoint, data from the analysis of sleep duration as a secondary endpoint (as well as any of the other secondary sleep endpoints) would have been viewed as supportive of a demonstration of an effect of DPH on sleep.

Turning now to the actual data for sleep duration, study 98-01 demonstrated a statistically significant difference between the combination and ibuprofen alone, suggesting an effect of DPH on sleep duration. These data would normally be considered hypothesis generating since they were seen in a study where there was no significant difference observed for the primary sleep endpoint for the critical comparison between the combination and ibuprofen. An appropriate response to this finding would have been to design additional clinical trials to explore sleep duration as a primary endpoint. As noted above, not only would such trials have been expected not to include forced awakenings, but the Agency also would have expected the patient reported data for sleep duration to be analyzed as a continuous variable. Instead, WCH chose to amend the analysis plan for study 98-02 to elevate sleep duration to be a primary endpoint along with sleep latency. While the records appear to indicate that this change was appropriately executed before the study blind for study 98-02 was broken, the resulting data must be interpreted in light of the design and analysis flaws stated above. So, while I concur with the sponsor that the combination was statistically significantly superior to ibuprofen alone for sleep duration in study 98-02, I also concur with the divisions and office that this finding is not sufficient to demonstrate the effect of DPH and thus, is not sufficient to support approval.

WCH argues that the Agency is applying too high a standard for approval for this product and implies that the standard for approval for an OTC drug should be lower than those applied to a prescription drug. I do not concur with WCH's argument. The evidentiary standard for approval of an OTC product is not lower than the standard for approval of a prescription drug. Advil PM is a new fixed-dose combination of an analgesic and a sleep aid for a new indication that has not previously been approved by FDA and must meet the same evidentiary standard normally applied to approvals under a NDA. WCH also argues that the Agency should accept one positive study and one supportive study for this application, as contemplated under FDAMA. While I agree that in some cases the Agency can base approvals on one positive study along with supporting evidence, the Agency would expect and require that the data from the single positive study provide substantial evidence of effectiveness.<sup>4</sup> As I have noted above, the data from the phase 3 studies supporting the contribution of DPH to the claimed effects of Advil PM do not rise to this standard and, therefore, do not support approval of Advil PM for the proposed indication.

#### Agency Expectation of Consistency Between Sleep Endpoints

You also argue that by expecting to see consistency for sleep endpoints, as noted in the approvable letter, the Agency is imposing an unnecessary and inconsistent standard for approval. I agree that it would not be necessary to demonstrate an effect of DPH on both sleep latency and

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<sup>4</sup> The Agency's current views on the use of a single positive clinical trial along with supporting evidence to support approval of an application are reflected in the "Guidance to Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products."

sleep duration in order to gain approval. Substantial evidence of an effect of DPH in the combination on sleep duration, from an adequate and well-controlled study designed with sleep duration as a primary endpoint, in addition to the data already presented in the original NDA, would in my view be sufficient for approval.<sup>5</sup>

That said, I believe that WCH has misinterpreted the divisions' concerns with regard to the need for a showing of consistency of endpoints. I do not believe the divisions intended this to mean a requirement that an effect be demonstrated for DPH on both sleep latency and sleep duration. Rather, I believe the divisions were simply referencing the findings in study 98-02 of a numerical advantage of ibuprofen alone over the combination for sleep latency. Such an unexpected result, if repeated in the requested additional study, would raise serious questions regarding whether the addition of DPH adversely impacts on the beneficial effect of ibuprofen on sleep latency in this population of patients. This is a valid regulatory concern, given that 21 CFR 330.10(a)(4)(iv) clearly states that a combination of two or more active ingredients should not decrease the safety or effectiveness of one or more of the active ingredients.

#### Conclusions

I have carefully reviewed the information provided in the February 5, 2003, FDRR and Agency documents related to these NDAs. For the reasons stated above, I do not concur with your assertion that an effect of DPH on sleep duration has been adequately demonstrated in the combination for the intended population of use. Therefore, I do not agree with your conclusion that the NDAs for Advil PM should be approved without additional clinical data. Your appeal, therefore, is denied. I concur with the divisions and the office that an additional adequate and well-controlled clinical study is necessary to clearly demonstrate that DPH contributes to the claimed effects of Advil PM. I also concur with the divisions and office that the additional study should be designed to assess both sleep latency and sleep duration with careful attention to study design, specifically avoiding waking the patients. While your request for immediate approval is denied, I concur with your assertion that it is not necessary that you demonstrate an effect of DPH on both sleep latency and sleep duration to support approval of the combination. Substantial evidence of an effect of DPH on sleep duration, in combination with the data already presented in this application, would be sufficient for approval, if the other deficiencies noted in the approvable letter are also satisfactorily addressed. I strongly encourage you to work with the divisions to design the new study and encourage you to consider submitting the study for Special Protocol Assessment before study initiation.

If you wish to appeal this decision to the next level, your appeal should be directed to Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research. The appeal should be sent again through the Center's Dispute Resolution Project Manager, Kim Colangelo.

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<sup>5</sup> This conclusion is based on the fact that WCH has provided substantial evidence that ibuprofen contributes an effect on pain relief and sleep latency in this population of patients.

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If you have any questions concerning your appeal or this letter, call Ms. Colangelo at (301) 594-5479.

Sincerely,

{See appended electronic signature page}

John K. Jenkins, M.D.  
Director  
Office of New Drugs  
Center for Drug Evaluation and Research

## ATTACHMENT 1

### SUMMARY REVIEW OF CLINICAL STUDIES<sup>6</sup>

#### Study 97-01

Study 97-01 was a pilot study with a full factorial design that evaluated the effects of ibuprofen alone, DPH alone, the ibuprofen/DPH combination, and placebo on endpoints related to pain and sleep in patients who had undergone recent dental surgery and who were experiencing pain and sleeplessness. Study 97-01 as designed was not adequately powered to reach definitive conclusions regarding the contribution of the individual components to the claimed effects of the proposed combination. The primary efficacy variables for study 97-01 were nurse observed sleep latency (NOSL) and the sum of pain relief plus pain intensity difference over the first three hours of the study (SPRID3). Secondary efficacy variables related to sleep and pain were also stated in the protocol. With regard to sleep, the secondary efficacy variables included ease of falling asleep, duration of sleep, global assessment of the study medication as a sleep aid, actual and cumulative proportions of subjects asleep at each observation point, and actigraphic assessments of sleep latency, total sleep time, and sleep efficiency.

The results of study 97-01 showed median NOSL of 30 minutes for placebo, 25 minutes for ibuprofen, 50 minutes for DPH, and 36 minutes for the combination. Statistical analyses of the data showed that ibuprofen alone was superior to placebo ( $p=0.033$ ), ibuprofen was superior to DPH ( $p=0.005$ ), and the combination was superior to DPH ( $p=0.019$ ). The combination was numerically better than placebo ( $p=0.068$ ), but the combination was not better than ibuprofen alone (in fact, it was actually numerically inferior) and DPH was not better than placebo. The failure of DPH alone to demonstrate an effect on sleep latency is at odds with the fact that DPH alone is considered to be an effective sleep-aid under the OTC monograph.<sup>7</sup> However, this finding is probably explained by the study entry requirements that patients be experiencing moderate or greater dental pain and sleeplessness. DPH is not a pain reliever and would not be expected to impact on the primary reason patients in this study had difficulty with sleep. The observation that ibuprofen alone was numerically better than the combination was also somewhat surprising, though it did not reach statistical significance. Looking at a secondary sleep endpoint, the cumulative percentage of patients asleep at 60 minutes, the results from study 97-01 were 57% for placebo; 77% for ibuprofen, 61% for DPH, and 90% for the combination. These secondary data appear to support the lack of effect of DPH alone on the primary sleep latency endpoint in this patient population, but in contrast to the NOSL data, suggest that the

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<sup>6</sup> The data and statistical analyses reported in this summary are derived either from the medical officer's primary review of the clinical studies or from the sponsor's FDRR package. In all cases, the p values reported are the nominal values and do not reflect any corrections for multiple comparisons. References to "significant" differences are based on observations of p values  $<0.05$ . The actual interpretability of the reported p values is heavily dependent on whether the comparison represented a pre-specified primary analysis or whether the p value reported is for a comparison that was a pre-specified secondary endpoint or post-hoc analysis. A statistically significant finding in-and-of itself is not sufficient to support a scientific conclusion or a regulatory decision.

<sup>7</sup> Per 21 CFR 338.50, the indications for DPH as an OTC sleep aid are "(1) ('Helps you' or 'Reduces time to') 'fall asleep if you have difficulty falling asleep.' (2) 'For relief of occasional sleeplessness.' (3) 'Helps to reduce difficulty falling asleep.'"

combination was better than ibuprofen alone. This latter effect may be evidence of an effect of the DPH component of the combination on sleep latency, but is not conclusive. The sleep duration assessment for study 97-01 showed a mean sleep score of 0.36 for placebo, 2.68 for ibuprofen, 0.23 for DPH, and 3.31 for the combination. These data also seem to confirm a lack of effect of DPH alone on sleep duration in this population, however, the finding that the combination was numerically greater than ibuprofen alone suggested a contribution of DPH to sleep duration as part of the combination.<sup>8</sup> With regard to pain, the SPRID3 data from study 97-01 demonstrated that both ibuprofen and the combination were significantly better than either placebo or DPH. The combination and ibuprofen alone were numerically similar and not statistically different for pain relief.

Overall, the results of study 97-01 reaffirmed that ibuprofen is an effective pain reliever in this population of patients and showed that DPH alone or as part of the combination had no effect on relief of pain. With regard to sleep, the results were less clear. Study 97-01 provided strong evidence that DPH alone is not an effective sleep aid in this patient population, however, any contribution of DPH in the combination to improved sleep latency or sleep duration was unclear and warranted further evaluation in larger studies with improved power to detect a difference.

#### Study 98-01

Based on the findings from study 97-01, WCH then developed two identical studies (98-01 and 98-02) to further evaluate the effects of the combination on parameters of pain and sleep and the contribution of DPH to the effects of the combination on sleep.<sup>9</sup> These studies were partial factorial designs in that they did not include the DPH alone treatment group since DPH was not expected to contribute to the relief of pain and this expectation was strongly supported by the data from study 97-01. The Agency apparently agreed to this partial factorial design and I concur that the design is acceptable since the primary question of interest was the contribution of DPH in the combination compared to ibuprofen alone. The overall design of studies 98-01 and 98-02 was very similar to study 97-01 and they were both conducted in patients with moderate or greater pain due to recent dental surgery and sleeplessness. The pre-specified primary efficacy endpoint for sleep was the cumulative percentage of subjects asleep at 60 minutes post-dosing based on nurse observations. The primary efficacy endpoint for pain was the SPRID2.<sup>10</sup> Secondary efficacy endpoints for sleep and pain were similar to those included in study 97-01.

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<sup>8</sup> The design of study 97-01 required that the patients be questioned about pain at 90, 120, and 180 minutes after study drug administration. The patient's reported duration of sleep was captured in categories (e.g., less than 5 hours, 5-6 hours, 6+ to 7 hours) rather than as a continuous variable. The validity of this study design for the assessment of sleep duration has been questioned by the divisions since it tends to group sleep duration scores that could be individually very different into the same category. For example, a total sleep time reported by the patient of 2 hours would be categorized the same as a total sleep time of 4.5 hours. I concur with the divisions' concerns about the validity of the study design and analyses for study 97-01 (as well as studies 98-01 and 98-02) with regard to sleep duration. The concerns severely limit the conclusions that can be drawn from these studies with regard to any effect of DPH in the combination on sleep duration.

<sup>9</sup> While studies 98-01 and 98-02 were essentially identical as designed, the sponsor chose to change the analysis plan for study 98-02 prior to breaking the study blind based on their analysis of the results from study 98-01. Therefore, these two studies are discussed separately.

<sup>10</sup> In contrast to study 97-01, patients were questioned about pain at 90 and 120 minutes post-dosing in studies 98-01 and 98-02. Thus, the primary pain efficacy variable was SPRID from 0-2 hours rather than 0-3 hours.

The results of study 98-01 for the cumulative percentage of patients asleep at 60 minutes were 40% for placebo; 64% for ibuprofen, and 64% for the combination. Statistical analyses of these data showed that both the combination and ibuprofen were superior to placebo and showed no significant difference between the combination and ibuprofen. Thus, the study failed to demonstrate a contribution of DPH to sleep latency, the pre-specified primary endpoint, in this population but demonstrated a significant contribution of ibuprofen to this effect, presumably due to its proven ability to relieve pain, which was the primary reason the patients were unable to sleep. The only secondary sleep endpoint that suggested a benefit of the combination over ibuprofen was sleep duration, which was measured using the same categorical scale used in study 97-01. With regard to SPRID2, both the combination and ibuprofen were superior to placebo and not statistically different from one another.

Overall, study 98-01 failed to demonstrate a contribution of DPH to sleep latency, which was the pre-specified primary endpoint for the study. Study 98-01 provided evidence that ibuprofen improved sleep latency, presumably through relieving pain, which was the primary reason patients in this study had difficulty with sleep. The secondary analysis for sleep duration suggested a contribution of DPH to the combination. Such an analysis would normally be viewed as hypothesis generating since the primary hypothesis for the contribution of DPH on sleep was not confirmed by the study results. The Agency would normally expect a sponsor to further evaluate such hypothesis generating findings in additional adequate and well-controlled studies.

#### Study 98-02

As noted above, study 98-02 was essentially identical in design to study 98-01. After the data from study 98-01 were analyzed, however, WCH decided to change the analysis plan for study 98-02 to include sleep duration as a primary endpoint in addition to sleep latency. WCH proposed a sequential analysis plan for the critical comparison of the combination to ibuprofen alone for the two sleep primary endpoints. The analysis plan specified that the sleep duration endpoint would be evaluated first followed by the sleep latency endpoint. The analysis plan further specified that the sleep latency endpoint would be eligible for being declared significant only if the duration of sleep endpoint was significant at  $p < 0.05$ . WCH has provided documentation to the Agency in support their assertion that this change in analysis plan for study 98-02 was done before the database for the study was "locked" and before the data were un-blinded.

Based on the information provided and statements made by WCH representatives with regard to the timing of the change to the analysis plan for study 98-02, such a change in the analysis plan would be acceptable from a statistical perspective. It is important to note however, that the change in analysis plan came after the study was complete and the study was not well designed to assess sleep duration. The study as designed and executed was primarily focused on evaluating the cumulative percentage of patients asleep at 60 minutes (i.e., sleep latency) and SPRID2. Sleep duration was one of several secondary sleep endpoints. A well-designed prospective study to evaluate sleep duration would likely not have included forced awakenings

of patients during the sleep period. In addition, the Agency would expect that the data for duration of sleep would normally be assessed either through objective measures or by patient's subjective reports of the number of hours slept analyzed as a continuous variable, not as a categorical variable. Thus, while the change in analysis plan appears to have been executed in an acceptable manner, the decision to elevate sleep duration to a primary endpoint was not in keeping with how the study was designed or executed. The elevation of sleep duration to be primary sleep endpoint, therefore, raises legitimate scientific and regulatory questions about the interpretability of such data.

The results of study 98-02 for sleep duration showed a mean sleep duration score of 0.1 for placebo, 2.0 for ibuprofen, and 2.6 for the combination. Both the combination and ibuprofen were significantly better than placebo and the combination was significantly better than ibuprofen.<sup>11</sup> With regard to the second primary sleep endpoint, the cumulative percentage of patients asleep at 60 minutes, the results of study 98-02 showed 27.5% for placebo, 75.6% for ibuprofen, and 66.4% for the combination. Both the combination and ibuprofen were significantly better than placebo; however, the combination was numerically inferior to ibuprofen alone ( $p=0.112$ ).

WCH has argued that the numerical advantage of ibuprofen alone compared to the combination should not be of concern since the combination and ibuprofen were numerically very similar for the endpoint of cumulative percentage asleep at 60 minutes in study 98-01 and since the combination was numerically superior to ibuprofen alone on this endpoint in the pilot study 97-01. It is worth noting, however, that the combination was numerically inferior to ibuprofen alone for the endpoint of NOSL in study 97-01.

With regard to SPRID2 scores, study 98-02 showed that both the combination and ibuprofen were significantly better than placebo, however, the results surprisingly showed that ibuprofen alone was significantly better than the combination. WCH argues that this finding should not be of concern given the absolute magnitude of the difference in pain scores was small and not clinically significant and the fact that fewer patients in the combination group required rescue medication for pain compared to the ibuprofen group (but note that this finding was not statistically significant). Despite these arguments, it is interesting to note that in study 98-02 the statistically significant superiority of ibuprofen alone over the combination for relief of pain correlates pathophysiologically with the numerical superiority of ibuprofen alone over the combination for the cumulative percentage of patients asleep at 60 minutes. While it is possible

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<sup>11</sup> There has been considerable debate regarding the appropriate statistical analysis procedure for the evaluation of the sleep duration endpoint due to the nature of how the data were collected and analyzed (i.e., as a categorical variable). WCH's pre-specified analysis was an ANCOVA. FDA reviewers also suggested that the sponsor analyze the sleep duration data using the Cochran-Mantel-Haenszel (CMH) test using modified ridit scores. For the critical analysis of the effect of the combination compared to ibuprofen for sleep duration, both tests demonstrated statistically significant results ( $p=0.005$  by ANCOVA,  $p=0.009$  by CMH with modified ridits). In the Office Director's response to the first FDRR, a concern was raised that the comparison of the combination to ibuprofen for sleep duration in study 98-02 did not achieve statistical significance. I concur with WCH that the combination was statistically significantly better than ibuprofen alone for the analysis of sleep duration. From my review of the record, it appears that the Office Director's reference to a non-significant finding for this critical comparison was in error and was based on an incorrect statement in one of the primary reviews that was later corrected.

that these findings occurred by chance, it is also possible that the combination group experienced lesser degrees of pain relief and that translated into their having greater difficulty falling asleep than the ibuprofen alone group.

Overall, study 98-02 showed a significant effect of DPH in the combination on sleep duration. The findings for DPH on sleep duration in this study, however, must be interpreted with caution in light of the fact that the study was not well designed for evaluating sleep duration. Study 98-02 also provided unexpected results with regard to relief of pain.

#### Other studies

As previously noted, the other clinical studies submitted by WCH for Advil PM were not appropriately designed to address the issue of contribution of individual components to the claimed effect(s) of the combination. These studies will be briefly summarized here for completeness.

Study 98-03 was a dose response study to evaluate the effects of two different doses of the fixed-dose combination of ibuprofen and DPH. No dose response was observed in this study for sleep latency as measured by the cumulative percentage of patients asleep at 60 minutes, however, there was a suggestion of a dose response for sleep duration, a pre-specified secondary endpoint.<sup>12</sup> A significant dose response was demonstrated for SPRID2, however, the absolute magnitude of the difference was small.<sup>13</sup>

Study 98-04 evaluated the safety and efficacy of Advil PM compared to placebo in patients who experienced nighttime chronic or episodic tension-type headaches and accompanying sleeplessness. The study design and endpoints were similar to the other studies described above.

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<sup>12</sup> The sleep duration data in study 98-03 were collected and analyzed the same way they were in studies 97-01, 98-01, and 98-02.

<sup>13</sup> It is interesting to note that the absolute magnitude of the differences in mean SPRID2 scores for the two dose groups in study 98-03 were very similar to the absolute magnitude of the differences in mean SPRID2 scores for ibuprofen and the combination in study 98-02. WCH argues in the FDRR that the statistically significant difference observed for SPRID2 in study 98-02 is not clinically meaningful.

<sup>14</sup> The sleep duration data in study 98-04 were collected and analyzed the same way they were in studies 97-01, 98-01, and 98-02.



Study 97-08 was designed to evaluate the safety of two different strengths of Advil PM compared to Tylenol PM (acetaminophen and DPH) and placebo for 10 days. This study differed from the other studies described above in that it was a multiple-dose study and the fact that the study was conducted on an out-patient basis. In this study, patients took the first dose of study medication on a night when they were experiencing sleeplessness associated with a headache or minor aches and pains, but on subsequent nights they were instructed to take the study medication regardless of whether they were experiencing symptoms. This design is consistent with the primary goal of the study, which was to assess safety.

Efficacy assessments for sleep and pain endpoints were conducted after the first dose of study drug. The results of study 97-08 showed that the mean number of patient reported hours slept, when analyzed as a continuous variable, was significantly greater for all three active treatment groups compared to placebo. The data showed a trend for a dose response for Advil PM ( $p=0.051$ ) and superiority of the higher dose of Advil PM to Tylenol PM ( $p=0.045$ ). When these data were analyzed using the categorical sleep duration rating system used in the other studies discussed above, the numerical trends and statistical results were not entirely consistent with the data reported above. Under the categorical analysis, only the high dose Advil PM was superior to placebo; the low dose Advil PM and the Tylenol PM were not superior to placebo. The categorical data demonstrated the higher dose of Advil PM to be superior to Tylenol PM ( $p=0.018$ ) and a trend for a dose response for Advil PM ( $p=0.60$ ). The most striking differences between the two analyses (continuous variable versus categorical variable) were the p values for the comparison of the low dose of Advil PM to placebo (0.030 continuous, 0.121 categorical) and the comparison of Tylenol PM to placebo (0.004 continuous, 0.074 categorical).

With regard to pain relief, both the high dose Advil PM and Tylenol PM were significantly better than placebo, but the low dose Advil PM was not. There was a suggestion of a dose response for Advil PM, but no evidence of a difference between Advil PM and Tylenol PM.

Overall, study 97-08 by its design contributes nothing to the question at issue in the FDRR (i.e., the contribution of DPH to the combination effects on sleep), however it does clearly demonstrate the fact that analysis of sleep duration data by continuous and categorical methodologies can result in different statistical conclusions.

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/s/

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John Jenkins  
2/26/03 06:42:07 PM

February 11, 2003

Sharon C. Heddish  
Vice-President, Worldwide Regulatory Affairs  
Wyeth Consumer Healthcare  
5 Giralda Farms  
Madison, NJ 07940

Re: Formal Dispute Resolution Request  
NDA 21-393, 21-394  
Advil® PM Liquigels/Caplets

Dear Ms. Heddish:

Please allow this letter to serve as written confirmation of receipt of Wyeth Consumer Healthcare's Formal Dispute Resolution Request (FDRR) regarding the August 8, 2002, approvable letter for Advil® PM Liquigels/Caplets and your FDRR dated December 10, 2002, to which the Agency responded on January 10, 2003, upholding the approvable action.

Pursuant to the CDER/CBER Guidance to Industry "Formal Dispute Resolution: Appeals Above the Division Level," the Food and Drug Administration (FDA) has thirty (30) calendar days from the receipt date of the formal request to respond to the appeal. The FDA received Wyeth Consumer Healthcare's FDRR on February 6, 2003; therefore, FDA's response to this FDRR is due to Wyeth on or before March 7, 2003.

This FDRR has been forwarded for review to Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. We will be in contact with you should we have any questions or require any additional information.

If I can be of any assistance to you during this process, please do not hesitate to contact me at (301) 594-5479.

Sincerely,

*{see appended electronic signature page}*

Kim M. Colangelo  
Formal Dispute Resolution Project Manager  
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**  
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/s/

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Kim Colangelo  
2/11/03 11:52:56 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-393/4

Wyeth Consumer Healthcare  
Attention: Ms. Sharon C. Heddish, Vice President  
Worldwide Regulatory Affairs  
Five Giralda Farms  
Madison, NJ 07940

Dear Ms. Heddish,

Please refer to your new drug applications (NDAs) submitted under Section 505(b) of the Federal Food Drug and Cosmetic Act for Advil®PM Liquigels (ibuprofen/diphenhydramine HCl/citrate).

NDA 21-393/4 proposed over the counter (OTC) use for the following claims: relief of occasional sleeplessness when associated with — minor aches and pains; and helps you get to sleep —

Wyeth was issued an approvable letter on August 8, 2002, for NDA 21-393/4, stating that the pivotal study, Study 98-02, in the drug development program does not adequately support the efficacy of this product for the proposed OTC use. Inconsistencies were cited in the results of the primary sleep endpoints, sleep latency (cumulative percent asleep at 60 minutes) and sleep duration. Notably, for sleep latency, ibuprofen was found to be numerically superior to the combination of ibuprofen/diphenhydramine, a difference which almost achieved statistical significance ( $p=0.1$ ). For sleep duration, the combination demonstrated superiority to ibuprofen. Subsequently, a post action meeting was held on September 12 to discuss the clinical issues raised in the approvable letter.

Your December 10, 2002, request for formal dispute resolution proposes that the NDA contains ample evidence to show that the combination of ibuprofen and diphenhydramine for the indication of relieving pain and accompanying sleeplessness is safe and effective, and that each active ingredient makes a contribution to the claimed effects. The "Grounds for Appeal" asserts that the NDA should be approved and that there is no need for any further studies.

**Dispute Issue: Whether an OTC product containing both ibuprofen and diphenhydramine and indicated for pain and accompanying sleeplessness satisfies the combination policy for OTC drugs.**

The proposed labeling claim is “for relief of occasional sleeplessness when associated with — minor aches and pains; helps you get to sleep — . This claim necessitates evidence of a contribution to efficacy for both improved latency (helps you get to sleep) as well as maintenance of sleep —

I agree that the combination of ibuprofen and diphenhydramine may provide rational concurrent therapy in a population of consumers suffering from both pain and accompanying sleeplessness. Both regulations cited, that for combination OTC products, 21 CFR 330, and that for prescription drug products, 21 CFR 300.50(a), require that each active ingredient of a combination make a contribution to the claimed effect.

Although Wyeth has submitted the results for a total of six studies, it is noted that only three of these studies involve comparisons of the combination with at least one of the component active ingredients. In essentially all instances, the data for sleep latency suggest that the effect observed favors the ibuprofen component. In none of the studies is the evidentiary standard for a contribution met for the diphenhydramine HCl component for sleep latency.

With regard to sleep duration, the pivotal study, 98-02, has limitations for the evaluation of contribution due to the partial factorial design and the lack of a diphenhydramine comparator arm. Concerns remain in this assessment as to the statistical robustness of the finding for sleep duration for this study. When analyzed sequentially, as was agreed to, using a more appropriate categorical Chi-square test rather than ANOVA, there is a p value of 0.242 for sleep duration. Finally, only one study in your submission, 97-01, had a full factorial design and did not demonstrate a benefit for diphenhydramine for sleep duration.

Although diphenhydramine HCl is established under OTC regulations 21 CFR 338.10 as a nighttime sleep aid, in the populations targeted by Wyeth in the submitted studies, the contribution of the diphenhydramine HCl component has not been established. Therefore, based on the submitted studies, Wyeth has not provided substantial evidence of efficacy for the proposed combination product based on regulatory standards for combination products, regardless of OTC or prescription status.

## **Conclusions**

I have reviewed your appeal and conclude that the data submitted in the NDA does not provide a sufficient basis for the approval of this combination drug product for the proposed marketing claim. Therefore, I am denying your request for dispute resolution to approve NDA 21-393/4 based on the submitted studies. This denial is based on insufficient evidence to substantiate contributions of component active ingredients to the sleep claims. I recommend that Wyeth discuss with the divisions an additional study to demonstrate the contribution of the diphenhydramine HCl component for the proposed claim and target population. If an additional study provides compelling evidence of the contribution of diphenhydramine HCl, the previously submitted studies may potentially provide adequate supportive data sufficient for replication.

If you wish to appeal this decision to the next level, your appeal should be directed to John Jenkins, M.D., Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent again through the Center's Dispute Resolution Project Manager, Ms. Kim Colangelo at (301) 594-5479.

If you have any questions, call Kim Colangelo, Formal Dispute Resolution Project Manager, at (301) 594-5479.

Sincerely,

Jonca Bull, M.D.

Office of Drug Evaluation V

Office of New Drugs

Center for Drug Evaluation and Research

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/s/

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Jonca Bull  
1/10/03 03:34:37 PM



NDA 21-393  
NDA 21-394

Wyeth Consumer Healthcare  
Attention: Sharon C. Heddish  
Vice President, Worldwide Regulatory Affairs  
Five Giralda Farms  
Madison, NJ 07940

Dear Ms. Heddish:

We acknowledge receipt on December 11, 2002, of your December 10, 2002, request for formal dispute resolution concerning the new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil PM. This request concerns scientific issues related to the adequacy of the efficacy and safety data submitted to NDA 21-393 (liquid dosage form), and cross-referenced by NDA 21-394 (caplet) to support the approval for the proposed indications. You are requesting the approval of Advil PM for relief of occasional sleeplessness when associated with — minor aches and pains, and to help the user to get to sleep —

Pursuant to the CDER/CBER Guidance to Industry "Formal Dispute Resolution: Appeals Above the Division Level," we have thirty (30) calendar days from the receipt date of the formal request to respond to the appeal. Therefore, our response to this request is due on or before January 10, 2003.

We acknowledge your request to have this appeal reviewed by Dr. John Jenkins, Director, Office of New Drugs. The decision which you are appealing was communicated to you in approvable letters (dated August 8, 2002) signed by Dr. Lee Simon, Director, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, and Dr. Charles Ganley, Director, Division of Over-The-Counter Drug Products. However, pursuant to the aforementioned guidance document, this matter should be formally reviewed by the next supervisory level, Dr. Jonca Bull, Director, Office of Drug Evaluation V, and therefore, has been forwarded to her. We will contact you should we have any questions or require additional information.

If you have any questions, please contact me at (301) 594-5479.

Sincerely,

*(See appended electronic signature page)*

Kim M. Colangelo  
Formal Dispute Resolution Project Manager  
Center for Drug Evaluation and Research

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/s/

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Kim Colangelo  
12/19/02 03:55:58 PM

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <b>21-393</b>	Efficacy Supplement Type <b>SE-</b>	Supplement Number.
Drug: <b>ibuprofen 200 mg / diphenhydramine HCl 25 mg</b>		Applicant: <b>Wyeth Consumer Healthcare (formerly Whitehall-Robins Healthcare)</b>
RPM: <b>Jane A. Dean, RN, MSN</b>		HFD- <b>550</b> Phone # <b>301-827-2536</b>
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): <b>NA</b>
❖ Application Classifications:		
<ul style="list-style-type: none"> <li>• Review priority</li> <li>• Chem class (NDAs only)</li> <li>• Other (e.g., orphan, OTC)</li> </ul>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <b>NSAID (5030300)</b> <b>NA</b>
❖ User Fee Goal Dates		<b>16 August 2002</b>
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
<ul style="list-style-type: none"> <li>• User Fee</li> <li>• User Fee waiver</li> </ul>		<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
<ul style="list-style-type: none"> <li>• User Fee exception</li> </ul>		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> <li>• This application is on the AIP</li> <li>• Exception for review (Center Director's memo)</li> <li>• OC clearance for approval</li> </ul>		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
<ul style="list-style-type: none"> <li>• Information: Verify that patent information was submitted</li> <li>• Patent certification [505(b)(2) applications]: Verify type of certifications submitted</li> </ul>		<input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).</li> </ul>		<input type="checkbox"/> Verified

Exclusivity (approvals only)	
• Exclusivity summary	NA
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	( ) Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
❖ Actions	
• Proposed action	( ) AP ( ) TA (X) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NA
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling	NA
• Original applicant-proposed labeling	NA
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	NA
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	NA
• Reviews	NA
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	NA
• Pre-NDA meeting (indicate date)	1 December 2000
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	NA

<b>Advisory Committee Meeting</b>	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	HFD-550 7 August 2002 HFD-560 7 August 2002
<b>Initial Indication</b>	
❖ Clinical review(s) (indicate date for each review)	6 March 2002 5 April 2002 10 May 2002
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	NA
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	NA
❖ Demographic Worksheet (NME approvals only)	NA
❖ Statistical review(s) (indicate date for each review)	30 April 2002
❖ Biopharmaceutical review(s) (indicate date for each review)	17 August 2001
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	NA
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	2 July 2002
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	2 July 2002
• Review & FONSI (indicate date of review)	NA
• Review & Environmental Impact Statement (indicate date of each review)	NA
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	2 July 2002
❖ Facilities inspection (provide EER report)	Date completed: 15 April 2002 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
<b>Nonclinical Pharmacology Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	11 April 2002
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NA
❖ CAC/ECAC report	NA

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/s/

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Jane Dean

8/7/02 04:48:54 PM

**MEMORANDUM**

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

**DATE:** 7 August 2002  
**FROM:** Jane A. Dean, RN, MSN, HFD-550  
**SUBJECT:** Advisory Committee Meeting for NDA 21-393

There was no Advisory Committee meeting for this NDA.

**MEMORANDUM**

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

**DATE:** 7 August 2002  
**FROM:** Jane A. Dean, RN, MSN, HFD-550  
**SUBJECT:** Federal Register Notices for NDA 21-393

There were no Federal Register notices for this NDA.

**MEMORANDUM**

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

**DATE:** 7 August 2002  
**FROM:** Jane A. Dean, RN, MSN, HFD-550  
**SUBJECT:** DSI Audit for NDA 21-393

There was no DSI audit of this NDA.

**MEMORANDUM**

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

**DATE:** 7 August 2002  
**FROM:** Jane A. Dean, RN, MSN, HFD-550  
**SUBJECT:** Pediatric Page for NDA 21-393

The Pediatric page is not applicable for this NDA at this time.

**MEMORANDUM**

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

**DATE:** 6 August 2002  
**FROM:** Jane A. Dean, RN, MSN, HFD-550  
**SUBJECT:** Package Insert for NDA 21-393

There is no package insert for this NDA.

**MEMORANDUM**

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

**DATE:** 6 August 2002  
**FROM:** Jane A. Dean, RN, MSN, HFD-550  
**SUBJECT:** Advertising for NDA 21-393

Advertising is not applicable for this NDA.

**MEMORANDUM**

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

**DATE:** 6 August 2002  
**FROM:** Jane A. Dean, RN, MSN, HFD-550  
**SUBJECT:** Post-marketing Commitments for NDA 21-393

There are no post-marketing commitments for this NDA.

**MEMORANDUM**

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

**DATE:** 6 August 2002  
**FROM:** Jane A. Dean, RN, MSN, HFD-550  
**SUBJECT:** Exclusivity Summary for NDA 21-393

An exclusivity summary is not applicable for this NDA. (2) This time (AE action)

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Ms. Mary Davis

**From:** Ms. Jane A. Dean, RN, MSN

**Fax:** 973-660-7187

**Fax:** 301-827-2531

**Phone:** 973-660-5825

**Phone:** 301-827-2090

**Pages:** (including cover page) 5

**Date:** 2 August 2002

**Re:** NDA 21-393 and NDA 21-394 Meeting Minutes for 4-24-02

**Urgent**  **For Review**  **Please Comment**  **Please Reply**  **Please Recycle**

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● **Comments:**

Dear Mary, here are the finalized minutes from the 4-24-02 meeting held here. Thank you for your patience in receiving them.

Sincerely,

Jane A. Dean  
Project Manager

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/s/

-----  
Jane Dean  
8/2/02 03:09:34 PM  
CSO

Wyeth Consumer Healthcare  
5 Giralda Farms  
Madison, NJ 07940

Mary H. Davis  
Director, Regulatory Affairs

973 660 5825 tel  
davism@wyeth.com

**Wyeth**

**ORIGINAL**

**RECEIVED**

**JUL 11 2002**

July 9, 2002

**MEGA/CDER**

**NDA 21-393**

**Ibuprofen 200 mg/Diphenhydramine HCl 25 mg Liquigels (OTC)**

**General Correspondence: Response to Statistical Questions-6/11/02 Teleconference**

Lee S. Simon, M.D., Director  
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTENTION: Document Control Room  
9201 Corporate Blvd.  
Rockville, MD 20850

*es C (corresponden*  
**ORIG AMENDMENT**

Dear Dr. Simon:

Reference is made to NDA 21-393 for ibuprofen 200 mg/diphenhydramine HCl 25mg liquid filled capsules (OTC) sponsored by Wyeth Consumer Healthcare (WCH). Reference is also made to our teleconference of 11 June 2002 with the agency. During that teleconference the Agency raised additional issues which we have attempted to address in the first attachment to this letter.

Specific aspects of the clinical studies that support this application have been discussed with the Agency over the last two months in a somewhat fragmented manner without considering the merits of the program in its entirety. Therefore, in addition to a response to specific questions raised during the teleconference of 11 June, the second document in this submission is a brief overview of the NDA clinical studies. It highlights the sequence of events, agreements reached with FDA and how WCH came to select "duration" as the primary endpoint. WCH continues to feel that these studies support approval of the NDA.

During the June 11 teleconference, it was apparent that the Agency continued to have multiple concerns about the application. Given that differences of opinion between the sponsor and the Agency regarding the application had not been resolved, we solicited the opinion of \_\_\_\_\_ Ph.D. a prominent statistical expert. We wanted an objective view of the application from someone who has experience in the OTC area. Dr. \_\_\_\_\_ is well known to FDA \_\_\_\_\_

# Wyeth

Agency. After thorough review of the Advil PM data, Dr. [redacted] concludes that the set of results offered presents a substantial case and is adequate for approval of the NDA. Dr. [redacted] letter is the third document in this submission.

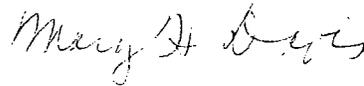
WCH invited comment on sleep parameters from [redacted] Ph.D. Dr. [redacted] is a renowned researcher in the area of sleep. Dr. [redacted] has reviewed the methods used to evaluate sleep latency and duration and concludes that WCH's approach was valid. He concluded that the categorical scale WCH used for sleep duration was appropriate for measuring total sleep time. His opinion agrees with the opinions of the expert statistical consultants who also support the analytical approach used by WCH.

WCH respectfully requests that you take this information into consideration as you render a decision on the application. At each step of the way, we have listened carefully to the Agency's concerns and have consulted with individuals with expertise pertinent to the question posed. In all, Drs. [redacted] have been consulted regarding clinical and statistical issues. Input from these experts has been consistent and supportive of WCH's position that the clinical data provided supports the approval of this NDA.

If there are any questions or comments regarding this submission, please contact the undersigned at (973) 660-5825 or Sharon Heddish at (973) 660-5753.

Sincerely,

WYETH CONSUMER HEALTHCARE



Mary H. Davis  
Director, Regulatory Affairs

**Note:** This submission is an electronic submission. The entire submission is presented in an electronic format. The size of this submission in MB as well as Virus Scan information is appended to this letter. Additionally, desk copies of this submission will be provided to the individuals copied on this letter.

Cc:

J. Dean, Project Manager HFD 560  
C. Ganley, MD, Director, HFD 560  
R. Katz, MD, Director, HFD 120  
C. DeBellas, Chief, Project Management, HFD 550  
J. Bull, MD, Director, ODE V

Division of OTC Drug Products Labeling Review

NDA 21-393

Submission Date: October 16, 2001

Review Date: July 9, 2002

Applicant's Representative: Mary Davis  
Director, Regulatory Affairs  
Wyeth Consumer Healthcare  
Five Giralda Farms  
Madison, NJ 07940  
973-660-5825

Drug: Advil®PM Liquigels  
(Solubilized Ibuprofen 200 mg./Diphenhydramine hydrochloride 25 mg Liquid Filled Capsules)

Pharmacologic Category: analgesic/nighttime sleep-aid

Submitted: Carton Labels for package count sizes of 4, 32, and 4 for physicians  
Blister Pack Labels for 4 and 8-count sizes  
Other (Booklet AP60011) Label  
Gravity feed and Shelf Tray labels

**Background:**

Diphenhydramine citrate and diphenhydramine hydrochloride are Category 1 single ingredient nighttime sleep-aids under 21 CFR 338 - Nighttime Sleep-Aid Drug Products for Over-the-Counter Human Use. A drug product containing a monograph analgesic (acetaminophen) in combination with a diphenhydramine salt is currently marketed pending a final monograph for OTC nighttime sleep-aids. The sponsor is now seeking approval to market the OTC combination of ibuprofen 200 mg with diphenhydramine HCl 25 mg in a liquigel dosage form.

A full review of the labeling will not be undertaken until the sponsor has submitted information to support the efficacy of ibuprofen 400 mg and diphenhydramine HCl 50 mg in a fixed combination oral liquid-filled capsule in relieving occasional sleeplessness when associated with — minor aches and pain. At such time, additional labeling (e.g., Indications and Warnings) may be needed. This is a preliminary labeling review.

Reviewer recommended additions are identified by "redlining" (shaded text) and deletions are identified by "strikeout."

**Reviewer's Comment:**

A. Carton Label [4-, — , 32-, — and 4- (for physicians) counts]:

I. Principal Display Panel

**Reviewer's comment:** This promotional statement must be deleted. It is



NEW!

**Reviewer's comment:** the word can remain for 6 months from date first marketed.

Advil<sup>®</sup> PM

Solubilized Ibuprofen, 200 mg/ Diphenhydramine HCl 25 mg Capsules  
Pain Reliever/ Nighttime Sleep-Aid

Qty. Liquid Filled Capsules

Advil PM ( ) Liquid Filled Capsules (on banner)

II. Drug Facts

---

*Drug Facts*

---

<i>Active ingredients (in each liquid filled capsule)</i>	<i>Purpose</i>
Diphenhydramine hydrochloride 25 mg .....	Nighttime sleep-aid
Solubilized Ibuprofen equal to 200 mg ibuprofen..... (present as the free acid and potassium salt)	Pain reliever

---

*Uses*

- for relief of occasional sleeplessness when associated with minor aches and pains
- helps you get to sleep and

**Reviewer's comment:** We will reserve comment on this section until the sponsor has demonstrated efficacy for quality and duration of sleep.

---

*Warnings*

**Allergy alert:** Ibuprofen may cause a severe allergic reaction which may include:

1   Page(s) Withheld

   § 552(b)(4) Trade Secret / Confidential

   § 552(b)(5) Deliberative Process

   ✓ § 552(b)(4) Draft Labeling

- adults: take 2 capsules at bedtime.
- do not take more than 2 capsules in 24 hours,

---

***Other information***

- read all warnings and directions before use. Keep carton.
- store at 20-25°C (68-77°F)
- avoid excessive heat 40°C (above 104°F)

---

***Inactive ingredients***

D&C red no. 33, FD&C blue no. 1, fractionated coconut oil, gelatin, lecithin, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan, sorbitol

---

***Questions or comments? Call 1-800-88-ADVIL***

**Reviewer's comment:** It is recommended that the days of the week and the times of the day when someone is available to respond to questions be included.

---

III. Side Panels (Left/Right depending on carton size)

**Reviewer's comment:** Same comment as A I above.

NEW!

**Reviewer's comment:** Same comment as A I above.

Advil® PM

**Reviewer's comment:** data not shown to support sticken words. The sponsor's claim of

**Product inside sealed in plastic blister with foil backing.  
Do Not Use if plastic blister or foil barrier is broken.**

Dist. by ~~Whitehall Robins Healthcare~~, Wyeth Consumer Healthcare  
Madison, NJ 07940

**Reviewer's comment:** Change name (and address, if necessary).

Made in USA

**Reviewer's comment:** same comment as above.

UPC Code

Lot No.            Exp.

**B. Blister Pack for 4- and 8-counts:**

Advil® PM

Qty.

Solubilized Ibuprofen 200 mg/

Diphenhydramine HCl 25 mg Capsule

Allergy — warning:

READ CARTON BEFORE USE.

Do Not Use if foil

barrier is broken.

Store at 20-25°C (68-77°F). Avoid excessive heat.

40°C (above 104°F). Protect from light.

Dist. by ~~Whitehall-Robins Healthcare~~ Wyeth Consumer Healthcare

R.P. Scherer Corp.

Made in USA.

LOT

EXP

PEEL & PUSH

**Reviewer's comment:** same comment as Carton Label (A III) above.

**C. Gravity feed dispenser label for 4-count size**

1. Product name (Advil PM)

**Reviewer's comment:** We encourage the inclusion of the established name and pharmacological categories as part of the statement of identity to appear at least once on the principal display panel.

2. Promotional Statements:

A.

**Reviewer's comment:** same comment as in Carton Label (A I) above.

- B. Promotional Statements appearing on 3 Panels

**Reviewer's comment:** According to the medical officer's review, the studies did not show that the combination was statistically significantly more effective for pain relief than ibuprofen alone. This statement must be deleted.

Helps you get to sleep and —

**Reviewer's comment:** This statement must be deleted unless the sponsor has demonstrated efficacy for quality and duration of sleep.

**Reviewer's comment:** same comment as Carton Label (A III) regarding . —

**Reviewer's comment:** same comment as in Carton Label (A I) above.

**Reviewer's comment:** The statement, if true, should be qualified by saying "---

3. Name and Place of Business

**Reviewer's comment:** need to change to reflect the new corporate name.

**D. Shelf tray label for 4-count size**

Principal Display Panel and 2 side panels:

a. Promotional Statement

**Reviewer's comment:** same comment as in Carton Label (A I) above.

b. "NEW"

**Reviewer's comment:** same comment as in Carton Label (A I) above.

c. Company name

**Reviewer's comment:** same comment as in Carton Label (A III) above.

E. Other: (Booklet AP60011) "Drug Facts" labeling is in 5 panels.

**Reviewer's comment:** We will reserve comment until a more detailed description explains the intent of the label.

**Recommendations:**

I. Inform the sponsor that a full review of the labeling will not be undertaken until the sponsor has submitted information to support the efficacy of ibuprofen 400 mg and diphenhydramine HCl 50 mg in a fixed combination oral liquid-filled capsule in relieving occasional sleeplessness when associated with — minor aches and pain. At such time, additional labeling (e.g., Indications and Warnings) may be needed. This is a preliminary labeling review.

**A. Carton Label:**

I. Principal Display Panel

Remove "  
statement must be deleted.

" This promotional

## II. Drug Facts Labeling

### a. Warnings:

- b. Questions or comments - the days of the week and times of the day when someone is available to respond to questions is recommended for inclusion.

## III. Side Panels

### a. Remove "

- b. Remove " There are no data to support the  
claim." The Sponsor's claim of

- c. Change the company name from Whitehall Robins Healthcare to Wyeth Consumer Healthcare.

## B. Blister pack for 4- and 8 counts:

Change the company name from Whitehall Robins Healthcare to Wyeth Consumer Healthcare.

## C. Gravity Feed Dispenser label for 4- counts:

a. The Agency encourages the inclusion of the established name and pharmacological categories as part of the statement of identity to appear at least once on the principal display panel.

b. Promotional Statements:

- \_\_\_\_\_ - This statement must be deleted unless the combination is shown to be statistically significantly more effective than ibuprofen alone.

- Helps you get to sleep \_\_\_\_\_ - This statement must be deleted unless the sponsor has demonstrated efficacy for quality and duration of sleep.

- \_\_\_\_\_ same comment as carton label regarding \_\_\_\_\_

- \_\_\_\_\_ This promotional statement must be removed. Same comment as in Carton Label (A I) above.

c. Add " \_\_\_\_\_ / \_\_\_\_\_

d. Change the company name from Whitehall Robins Healthcare to Wyeth Consumer Healthcare.

#### D. Shelf Tray label for 4-count size

a. Promotional Statements:

- \_\_\_\_\_ This statement must be deleted unless the combination is shown to be statistically significantly more effective than ibuprofen alone.

- Helps you get to sleep and \_\_\_\_\_ - This statement must be deleted unless the sponsor has demonstrated efficacy for quality and duration of sleep.

- \_\_\_\_\_ Same comment as carton label regarding \_\_\_\_\_

- \_\_\_\_\_ This promotional statement must be removed.

- b. Change the company name from Whitehall Robins Healthcare to Wyeth Consumer Healthcare.
- E. Inform the sponsor to delete the word "NEW" six months after introduction into the market place.
- F. For booklet AP60011, inform the sponsor that comment on it is reserved until a more detailed explanation of its intent is submitted.

*Michael T. Benson, R.Ph., J.D.*

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

*Marina Chang, R.Ph.*

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

*Rosemarie Neuner, M.D.*

Concurrence, Rosemarie Neuner, M.D., M.P.H  
Medical Officer.

**Meeting Minutes**

Meeting Date: June 11, 2002  
 Time: 4:10 PM - 5:00 PM  
 Location: 9201 Corporate Blvd., Room N351  
 Rockville, MD 20850  
 Application: NDA 21-393 and NDA 21-394  
 Type of Meeting: Teleconference  
 Meeting Recorder: Tia Frazier

**FDA Participants, Titles, And Office/Division**

<b>Participant</b>	<b>Title</b>	<b>Division Name &amp; HFD#</b>
1. Jonca Bull, M.D	Office Director, ODE V	ODE V, HFD-105
2. Charles Ganley, M.D.	Division Director	Division of Over-the-Counter Drug Products, HFD-560
3. Linda M. Katz, M.D., M.P.H.	Deputy Division Director	Division of Over-the-Counter Drug Products, HFD-560
4. Stan Lin, Ph.D.	Statistical Team Leader	Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
5. Kun Jin, Ph.D.	Statistical Team Leader	Division of Neuropharmacological Drug Products, HFD-120
6. Hong Lu, Ph.D.	Statistical Reviewer	Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
7. Tia Frazier	Regulatory Project Manager	Division of Over-the-Counter Drug Products, HFD-560
8. Carmen DeBellis	Supervisory Regulatory Project Manager	Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

**Wyeth Consumer Healthcare Participants**

<b>Participant</b>	<b>Title</b>
1. Roger Berlin, M.D.	President, Global Scientific Affairs
2. Steve Cooper, D.M.D., Ph.D.	Senior Vice President Clinical and Medical Affairs
3. Sharon Heddish	Vice President, Global Regulatory Affairs
4. Geraldine Doyle, Ph.D.	Senior Director, Clinical Affairs
5. Joel Waksman, Ph.D.	Biostatistics and Data Management
6. Mary Davis	Director, Regulatory Affairs
7. Dr. _____	Consultant
8. Dr. _____	Consultant
9. Tai liang Xie	Director, Biostatistics
10. Shymalie Jayawardena	Principal Statistician

**BACKGROUND:**

Deficiencies arising from the review of NDAs 21-393 and 21-394 were communicated in an April 24, 2002, meeting with Wyeth Consumer Healthcare (WCH). During this meeting, WCH requested a meeting with FDA statisticians to discuss the statistical issues related to the evaluation of study 98-02. On May 23, 2002, the firm provided written responses to key issues that they had identified in the April 24 meeting (Attachment). The responses addressed statistical and clinical issues and FDA concerns with implementation of the combination policy. The review divisions agreed to their original request to have a discussion of the statistical testing methods for the endpoint of sleep duration.

At the outset, FDA emphasized that the purpose of the teleconference was to discuss the statistical methodology and not to address the firm's responses to each of the "key issues" they identified from the April 24, 2002, meeting. FDA addressed overriding concerns with the statistical analyses and pivotal study design.

**Meeting Summary:**

The discussion focused on the statistical analysis of the duration of sleep endpoint in study 98-02. FDA outlined the problems related to the use of categories in describing the extremes of duration of sleep (i.e., less than 5 hours and greater than 9 hours) and how this could impact on the analysis and interpretation of the data. FDA raised concerns about the truncation of the duration of sleep to a category of "less than 5 hours" and the potential bias that can be introduced in group population means with this categorization when using the Mandel Haenzel Cochran (MHC) test. FDA has demonstrated by statistical simulation that the MHC test is sensitive to differences in two such group population means resulting from the truncation, which raises a particular concern about the use of a p-value based on the truncated sample. FDA stated that the sponsor needs to prove that the truncation used in this study did not introduce bias into the results. WCH noted that there is consistency in the data from several of the studies and there should be little cause for concern.

There was a brief discussion of problems related to the measurement of sleep duration. Subjects were awoken from sleep to self-assess their degree of pain, but FDA has concerns that this measurement was subjective and that the waking of subjects to assess pain ultimately affected duration of sleep.

FDA noted the apparent inconsistency between the results for the sleep latency and sleep duration endpoints in study 98-02. The results of this study indicate that while the combination improved sleep duration over the single ingredient, the combination did not improve sleep latency over the single ingredient. In fact, sleep latency was improved more with the single ingredient product than with the combination.

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FDA will determine in the review whether study AE-98-02 (and other data in the NDA) is sufficient to support efficacy.

**Action Item**

A time for further discussion of these new drug applications was requested by WCH but not agreed to by FDA. FDA is still having internal discussions to decide a course of action and, based on workload and likely outcome, does not believe additional discussions will be fruitful. The sponsor can submit additional information relevant to this statistical discussion. FDA will take this additional information into consideration if it is submitted with adequate time for review before an action is due.

ATTACHMENT: (1) WCH May 23, 2002, submission to NDAs

Drafted by: HFD-560/Frazier  
Initialed by: HFD-560/Ganley/7-18-02  
                  HFD-550/DeBellas  
                  HFD-710/K.Jin/7-18-02  
Final:       HFD-560/Hilfiker/7-18-02

MEETING MINUTES

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## **Attachment 1**

**May 23, 2002 submission  
WCH Response to initial FDA comments**

### **Introduction**

On April 24, 2002, a meeting was held between FDA and Wyeth Consumer Healthcare. FDA requested this meeting to express their concerns about the data supporting the efficacy of ibuprofen/diphenhydramine in the treatment of sleeplessness associated with — minor aches and pains. These data had been submitted to FDA on October 15, 2001, as part of NDA 20-393.

This document presents Wyeth's response to the Agency's concerns. The responses are based on previous agreements reached with the Agency, key efficacy data from the NDA (including a review and discussion of reanalyses of sleep duration using various statistical methods), and expert clinical opinion.

### **Concern #1**

The Agency did not agree with the "subjective" assessment of duration in the pivotal efficacy trials. In particular, there was concern that subjects were awakened (if necessary) during the evaluation period to assess pain, and this might affect the measure of duration.

### **Wyeth Response**

- The design of the pivotal efficacy studies (including the methodology for assessing sleep duration) had previously been reviewed with, and agreed to by the Agency.

The results from a pilot study (AE-97-01) conducted in the modified oral surgery model with phase advancement incorporated into its design were presented at a meeting held between the Agency and Wyeth on August 4, 1998. The protocol designs for the partial factorial, pivotal efficacy studies were also reviewed with the Agency at this meeting. The Agency was specifically asked "are the modified oral surgery and inpatient headache models, with phase advancement incorporated into the design, appropriate for evaluating the efficacy of analgesic/sleep-aid products?" As per FDA's minutes from that meeting, the Agency responded "A transient insomnia model, with phase advancement is not considered reliable. However, FDA recognizes this may be the only practical way to assess both sleep and pain endpoints." (note that the Agency had requested that pain and sleep be assessed in the same subject). Although the meeting also included a discussion of the appropriate primary endpoint for sleep efficacy (see below), the Agency did not express any concerns about how sleep efficacy was being assessed, including sleep duration. (Note: The Agency concurred that a partial factorial design which included placebo, ibuprofen alone, and the combination was appropriate for the pivotal trials. This was based on the results of the pilot study, which demonstrated that diphenhydramine alone was clearly not as effective as ibuprofen alone for either sleep efficacy or for pain relief. The explanation for this result is that the pain was not relieved by diphenhydramine, and it kept subjects from falling asleep, thus rendering it minimally effective. It was agreed that the key objective was whether the combination was better than ibuprofen alone for sleep efficacy).

- Wyeth acknowledges that awakening subjects in order to assess pain relief was not ideal, but it was the only viable alternative for measuring sleep and pain simultaneously. However, in order to minimize any sleep disruptions, pain assessments were done only twice, and limited to the first two hours after bedtime. Also, since all subjects were treated identically and the study was blinded, any bias in the measure of duration would have been distributed across all of the treatment groups. Furthermore, frequent nocturnal awakenings has been used by sleep experts as a model for evaluating insomnia. The fact that an advantage in sleep duration for the combination was demonstrated despite this additional disruption in sleep provides clear evidence of the contribution of diphenhydramine to the overall efficacy of the combination.
- The Agency's Guidance for the Clinical Evaluation of Hypnotic Drugs indicates that subjective assessments of sleep efficacy, including sleep duration, are acceptable for demonstrating the efficacy of products intended to relieve sleeplessness. Most of the studies supporting diphenhydramine's Category I status used subjective assessments to demonstrate its effectiveness. More recently, numerous prescription drugs, including the benzodiazepines and zolpidem, have been approved based, in part, on showing an advantage for the subjective assessment of sleep duration (as well as sleep latency). In addition, clinical trials have shown that subjective assessments correlate well with objective data. Our expert sleep consultant has provided a more in depth overview of the subjective assessment of sleep duration. The overview can be found in Appendix I.
- In our studies, duration of sleep was assessed by the subject using a 6 point categorical scale (0 = < 5 hours, 1 = 5-6 hours, 2 = 6-7 hours, 3 = 7-8 hours, 4 = 8-9 hours and 5 = > 9 hours). The FDA accepted this scale, but also requested (at a pre-NDA meeting held in December, 2000) that these data be rescaled for analytical purposes to the midpoint of each time range (2.5 hours, 5.5 hours, 6.5 hours, 7.5 hours, 8.5 hours, and 9.5 hours). As shown in Table 1, the results based on this revised scale were remarkably consistent with those from the original protocol specified categorical scale. Since individuals who sleep less than 6 hours are considered to have significant sleep disruption, a further analysis of the proportions of subjects who fell into categories 0 and 1 were also completed. Taken together, these three analyses (which were included in the individual study reports) support the robustness of the conclusion that diphenhydramine contributes to the combination by increasing the duration of sleep.
- The magnitude of the differences seen between the combination and ibuprofen alone for sleep duration (0.7 to 0.9 hours – rescaled data) are similar to differences demonstrated between zolpidem and placebo for this subjective assessment (0.55 to 0.77 hours). Zolpidem was approved in 1992 for the treatment of insomnia and is indicated to shorten sleep latency and improve sleep duration.

**Table 1. Interstudy Comparison of Sleep Duration Parameters from Oral Surgery Studies (ITT Subjects)**

Efficacy Parameter		Treatment Groups			Pairwise Comparisons ( $\Delta$ , p-value)		
		IBU/DPH 400/50 mg	IBU 400 mg	PBO	IBU/DPH vs PBO	IBU/DPH vs IBU	IBU vs PBO
<b>Sleep Parameters</b>	<b>Study</b>						
<b>Sleep duration # mean (s.d.)</b>	97-01 (pilot)	3.3 (1.9)	2.7 (2.1)	0.4 (1.3)	2.9 <0.001*	0.6 0.131	2.3 <0.001*
	98-01	2.8(2.1)	2.3(2.1)	0.3(0.8)	2.5 <0.001*	0.5 0.022*	2.0 <0.001*
	98-02	2.6(1.9)	2.0(1.8)	0.1(0.3)	2.5 <0.001*	0.6 0.005*	1.9 <0.001*
	98-03 (dose-response)	3.1 (1.9)	-	0.6(1.3)	2.5 <0.001*	-	-
<b>Re-scaled<sup>^</sup> Sleep duration - mean (s.d.) hours</b>	97-01 (pilot)	7.5(2.5)	6.7(2.8)	3.0(1.9)	4.5 <0.001*	0.8 0.125	3.7 <0.001*
	98-01	6.8 (2.8)	6.1 (2.8)	3.1(1.5)	3.7 <0.001*	0.7 0.042*	3.0 <0.001*
	98-02	6.7 (2.6)	5.8(2.6)	2.6(0.6)	4.1 <0.001*	0.9 0.006*	3.2 <0.001*
	98-03 (dose-response)	7.3 (2.5)	-	3.5 (2.1)	3.8 <0.001*	-	-
<b>% slept &lt;6 hours</b>	97-01 (pilot)	24.1	38.7	92.9	-68.8 <0.001*	-14.6 0.192	-54.2 <0.001*
	98-01	36.1	49.6	95.0	-58.9 <0.001*	-13.5 0.036*	-45.4 <0.001*
	98-02	37.0	48.0	97.5	-60.5 <0.001*	-11.0 0.092	-49.5 <0.001*
	98-03 (dose-response)	29.8	-	85.4	-55.6 <0.001*	-	-

$\Delta$  is the observed difference between the pair (first –second) of treatments; \*  $p \leq 0.05$  in favor of the first treatment listed.  
 # Per-protocol assessment used a categorical scale 0 (<5 hours) to 5 (> 9 hours)  
 ^ As requested by the Agency, re-scaled using mid-point of the recorded scale.

**Concern #2**

The Agency indicated that duration of sleep was specified as the primary sleep endpoint in only one of the two pivotal efficacy studies (AE-98-02). Since the protocol for the pivotal study AE-98-01 did not specify sleep duration as the primary endpoint, the Agency has downgraded the level of evidence it provides. Therefore, the Agency has concluded that Wyeth has only one pivotal study demonstrating the contribution of diphenhydramine to the overall efficacy of the combination.

**Wyeth Response**

- Wyeth acknowledges that duration was specified as the primary sleep endpoint in only one of the two pivotal studies. However, duration of sleep was clearly identified as an equally important endpoint in assessing sleep in all of the studies. In addition, the data from both pivotal trials, as well as the pilot oral surgery study (AE-97-01), and the dose-response study (AE-98-03) clearly indicate that diphenhydramine contributed to the overall effectiveness of the combination by prolonging the duration of sleep. The consistency of these findings across all of the studies is presented in Table 1 and Figure 1. It should be noted that although the pilot study was not powered to demonstrate statistical differences, the magnitude of treatment difference was remarkably consistent with the pivotal trials.

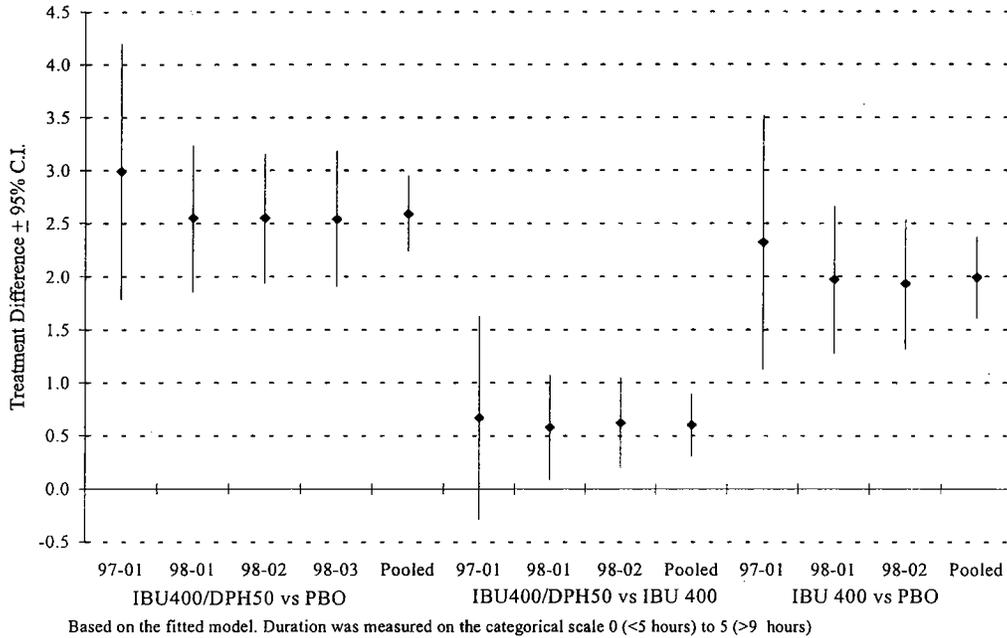
The consistency of the studies across another key efficacy measure, the proportion of subjects not needing rescue medication, is presented in Figure 2. These data further support the robustness of these studies, as well as the incremental benefit of the combination over ibuprofen alone.

- Although duration was specified as the primary endpoint in only one trial, at the August 4, 1998 meeting, the Agency itself indicated that: "sleep latency, duration of sleep, and sleep quality are the efficacy parameters for sleep evaluation. FDA will accept the sponsor's proposal of the percentage of patients asleep at 60 minutes (as the primary sleep endpoint), but all endpoints should be evaluated." Based on these comments, it is clear that the secondary efficacy measures should not be ignored.
- Also at that same meeting, the Agency went on to say that "... they would consider the data from one strong dental pain trial plus the data from the pilot study. However, FDA would prefer to receive data from two trials to clearly establish the product effectiveness..."

In addition, consistent with the Guidance for Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May, 1998), subsequent agreements reached with the Agency regarding the Clinical Development Programs for other combination products containing ibuprofen combined with a monographed product (ibuprofen/pseudoephedrine/chlorpheniramine for allergy, and ibuprofen/pseudoephedrine/dextromethorphan for cough/cold) have required just one clinical study supporting the efficacy and safety of the product.

Wyeth believes that the data from AE-98-01 cannot be ignored. However, even if the data from that trial are only considered as supportive, when taken together with the data from AE-98-02 and the pilot study, Wyeth believes there is strong evidence supporting the efficacy of the combination.

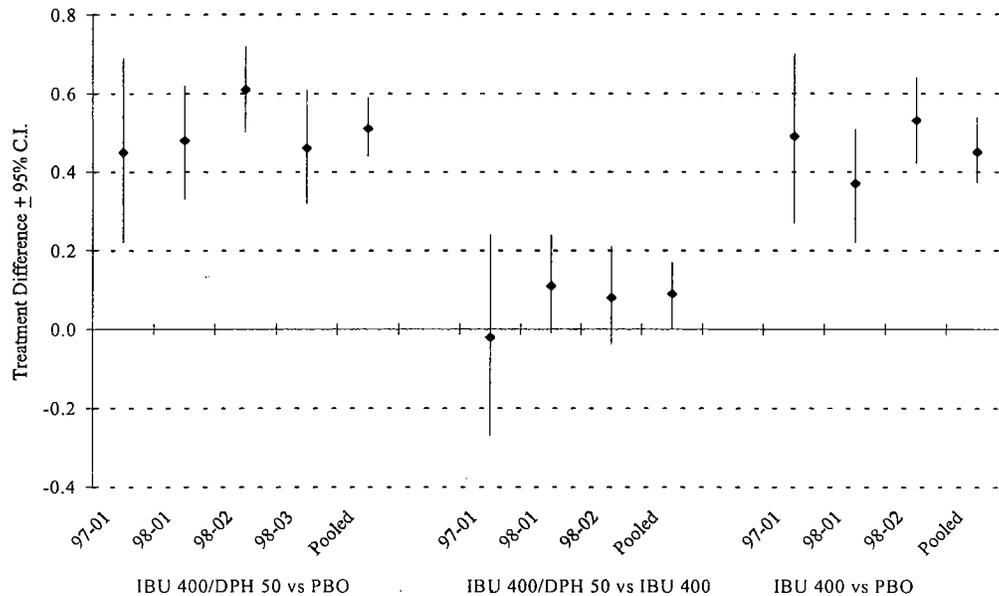
**Figure 1. Duration of Sleep (Categorical Scale) - 95% Confidence Intervals for the Pairwise Differences From The Individual and Pooled Oral Surgery Studies**



**Figure 2: % of Subjects Not Needing Rescue Medication - 95% Confidence Intervals for Pairwise Differences From The Individual and Pooled Oral Surgery**

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ON ORIGINAL**

### Studies



### Concern #3

The Agency questioned the “robustness” of the findings from AE-98-02, since statistically significant differences favoring ibuprofen/diphenhydramine compared to ibuprofen alone for duration of sleep was not demonstrated when the data were analyzed via the Cochran-Mantel-Haenszel (CMH) general association statistic.

### Wyeth Response

Each of the single dose efficacy protocols specified that duration would be analyzed via analysis of variance in a model containing treatment, baseline pain severity and gender effects. This analysis demonstrated the superiority of the combination over ibuprofen alone for sleep duration. However, in order to show the robustness of the results from the protocol specified analysis, the data were also analyzed via Cochran-Mantel-Haenszel test using the row mean score statistic with modified ridit scores, stratifying by baseline pain severity and gender. These results were included in the individual study reports submitted as part of the NDA.

The relevant statistical question was whether the combination of ibuprofen and diphenhydramine shifted the distribution towards the category indicating a longer duration of sleep (relative to ibuprofen alone) in these trials. Wyeth believes that the Cochran-Mantel-Haenszel (CMH) row mean score statistic, and not the CMH general association statistic, is an appropriate method for

testing this hypothesis, since it weights the categories (the column variable) consistent with ordering. The CMH general association statistic addresses the categories in an overall manner that ignores their ordering and tests the differences between distributions of treatment groups for *any combination* of categories. Furthermore, the general association statistic has the same value when categories are rearranged, and thereby it ignores the distinction between the good or bad outcomes which the categories represent. For this reason, the results from the row mean score statistic, rather than the results for the general association test, were presented in the study reports. Wyeth, as well as our expert statistical consultant (Appendix II), feels strongly that this is the more appropriate statistical model for ordinal data.

In order to further demonstrate the robustness of the finding that ibuprofen combined with diphenhydramine provided a longer duration of sleep relative to ibuprofen alone, several additional statistical procedures appropriate for testing ordered hypotheses were performed on these data. The results are shown in Table 3.

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**Table 3. Results Of Additional Analyses of Duration Data**

Test	Combo vs IBU p-value			Comment
	AE-98-01	AE-98-02	Pooled	
CMH analysis row mean score statistic using modified ridit scores	0.042	0.009	0.001	Data included in individual study reports. This procedure is equivalent to a stratified Wilcoxon-rank-sum test.
Goodman-Kruskal Gamma Statistic	0.042 ( $\gamma=0.187$ )	0.005 ( $\gamma=0.237$ )	0.001 ( $\gamma=0.212$ )	Indicates that the probability of observing a longer duration is significantly higher for any subject in the combo group compared to one in the IBU group.
CMH analysis row mean score statistic using FDA suggested scores for duration using table scores	0.055	0.012	0.002	FDA suggested scores were 2.5, 5.5, 6.5, 7.5, 8.5 and 9.5 based on the midpoint of each category
Logistic regression on cumulative odds <sup>1</sup>	0.042, (OR=1.62)	0.007, (OR=1.86)	0.001, (OR=1.70)	The odds of being in a higher category for duration (vs a lower category) is about 62% to 86% higher for those in the combo group compared to the IBU group

<sup>1</sup> For individual studies, results are based on the proportional odds model. (Statistical testing of the proportional odds assumption indicated the validity of this model.) For pooled studies, results were based on a partial proportional odds model with separate intercepts for each study.

All of these methods showed that the combination significantly increased the duration of sleep compared to ibuprofen alone (except for just missing significance for the CMH analysis with FDA suggested scores in AE-98-01). The magnitude of the benefit was substantial, as indicated by the high values of the summary statistics ( $\gamma$  and the odds ratios). Furthermore, these show that the results were consistent across the studies.

The robustness of these findings, both within and between studies, from procedures appropriate for testing ordered hypotheses, attest to the conclusion that the combination of ibuprofen and diphenhydramine helps individuals sleep longer than ibuprofen alone.

**Concern #4**

The Agency also expressed concerns with the data from AE-98-02 because ibuprofen alone was numerically better than the combination for measures of sleep latency and was statistically better for assessments of pain efficacy. In the view of the Agency, these results were contradictory and make the acceptability of Study AE-98-02 questionable.

**Wyeth Response**

- The finding that ibuprofen alone was slightly better than the combination for pain relief and sleep latency in AE-98-02 probably reflects the differences in the ibuprofen pharmacokinetic profiles of the formulations used in the pivotal efficacy studies. Two pharmacokinetic

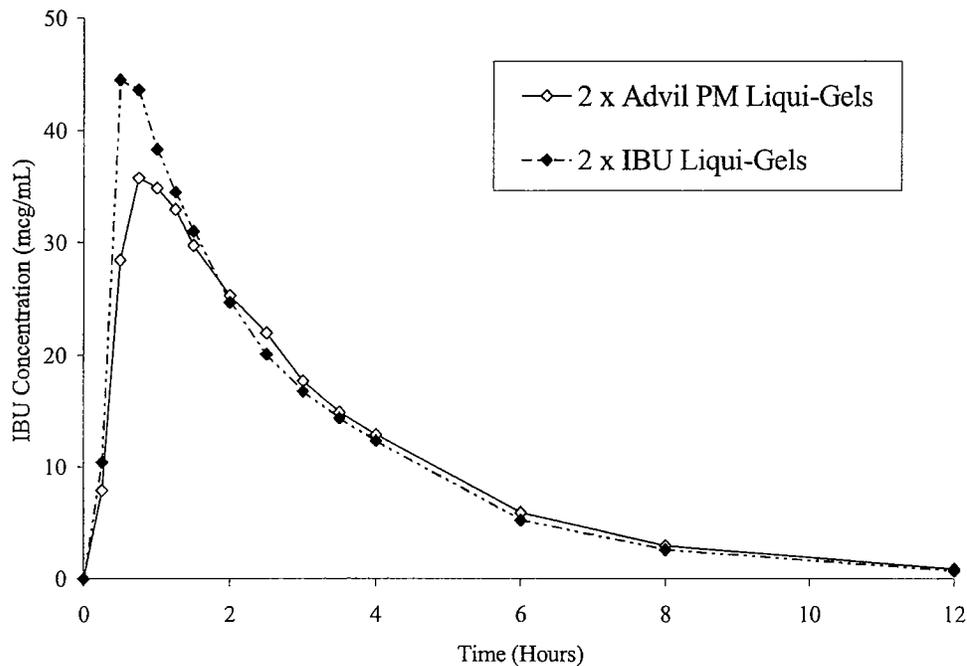
studies submitted as part of this NDA (AE-97-02 and AE-97-09) have shown that the T<sub>max</sub> of ibuprofen administered as a single ingredient liquigel formulation is 0.61 to 0.75 hours vs 0.9 to 1.0 hours for the combination formulation, and the C<sub>max</sub> is 45-48 mcg/mL, compared to 34-38 mcg/mL, respectively. Mean plasma ibuprofen concentration curves from study AE-97-09 are presented in Figure 3.

Although study AE-98-02 showed that single entity ibuprofen was significantly better than the combination for pain relief (as reflected by SPRID over 2 hours), the treatment differences were small, and not clinically relevant since a lower percentage of subjects who received the combination required rescue medication compared to those who received ibuprofen alone. Furthermore, in the other pivotal efficacy study AE-98-01, there were no differences favoring ibuprofen compared to the combination for pain relief.

Even if the single entity ibuprofen formulation provides slightly better pain relief than the combination product, the studies still show that the combination is a very effective pain reliever. More importantly, the trials demonstrate that the combination clearly provides a clinically relevant advantage to consumers compared to ibuprofen alone in terms of providing an improvement in the duration of sleep.

**Figure 3: Mean Ibuprofen Concentrations Following Administration of 2 x Ibuprofen/Diphenhydramine HCl 200/25mg Liquigels and 2 x Ibuprofen Liqui-Gels -Study AE-97-02 (n=25)**

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ON ORIGINAL**



#### **Concern #5**

The Agency also indicated that demonstrating that the combination was better than ibuprofen alone for duration, but not for sleep latency, was contradictory.

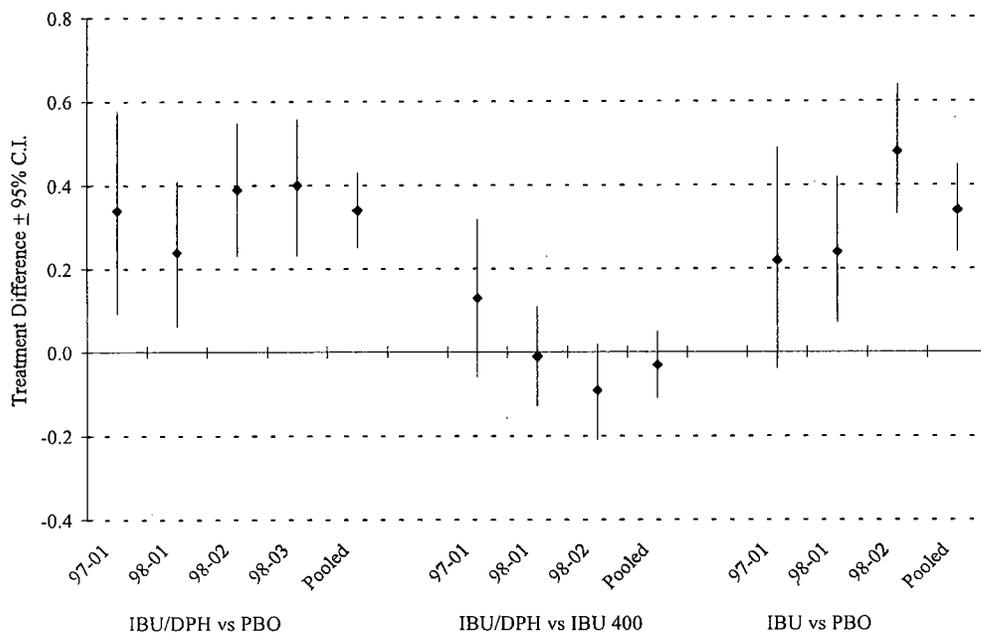
#### **Wyeth Response**

- The outcomes of the two pivotal and one pilot study were consistent with one another (Figures 1, 2 and 4) and clearly demonstrate that when ibuprofen is combined with diphenhydramine, the ibuprofen component drives sleep latency (as well as pain relief), and diphenhydramine contributes to the overall effectiveness of the combination by prolonging sleep duration.

These findings are due to the fast onset of action of ibuprofen, which results in pain relief within the first 30 minutes. For many individuals, relieving pain allows sleep onset to occur.

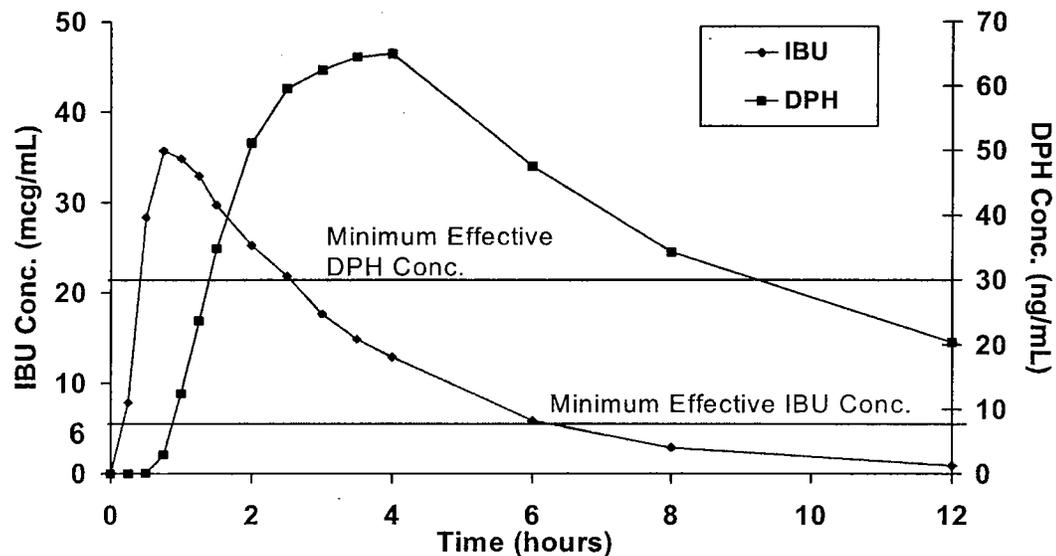
(Note: a study conducted in normal healthy subjects has shown that ibuprofen alone has no sedative effects.) In contrast, diphenhydramine influences duration of sleep, which results in a significantly better effect for the combination treatment compared to ibuprofen alone for this parameter. These results clearly correlate to the pharmacokinetic profiles of ibuprofen and diphenhydramine, as shown in Figure 5 and are in fact, not contradictory.

**Figure 4. Cumulative Percentage of Subjects Asleep by 60 Minutes - 95% Confidence Intervals for the Pairwise Differences from the Individual and Pooled Oral Surgery Studies**



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**Figure 5 – Study AE-97-02 Mean Ibuprofen and Diphenhydramine Concentrations Following Administration of 2 x Ibuprofen/Diphenhydramine HCl (200mg/25mg) Liquigels (n=25)**



### Conclusions

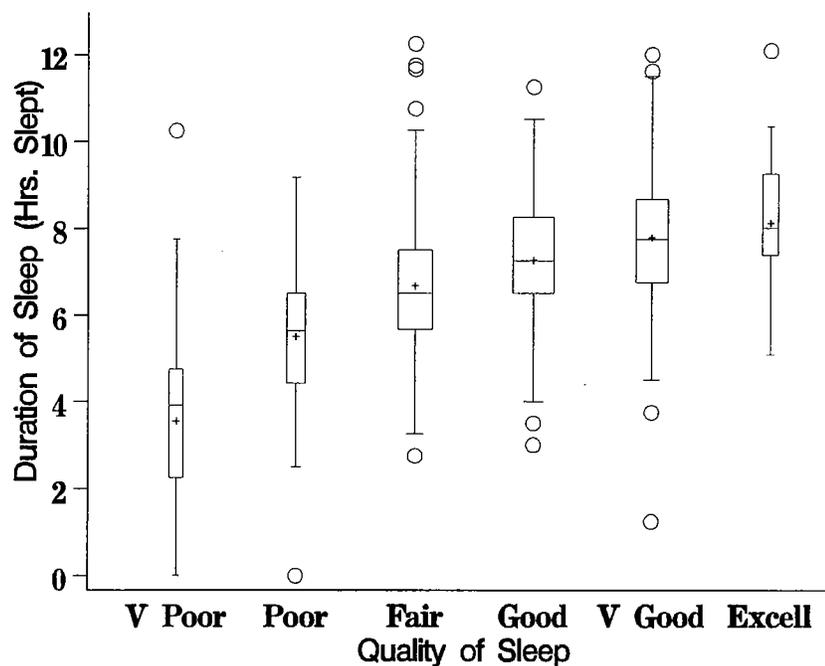
WCH hopes these responses address the Agency's concerns about the efficacy data submitted in support of the approval of ibuprofen combined with diphenhydramine for the treatment of sleeplessness associated with — minor aches and pains.

We have provided background information justifying that the models and methodologies used to evaluate the combination were appropriate. We also believe that we have provided you with substantial data clearly demonstrating that while both ibuprofen alone and ibuprofen combined with diphenhydramine are very effective in relieving pain and allowing for sleep to occur, the combination provides a clinically meaningful benefit of allowing individuals to sleep longer than taking ibuprofen alone. We have also provided you with various data demonstrating the consistency of these findings across the four oral surgery studies conducted as part of this program (two pivotal trials, one pilot study and a dose-response study).

In addition to these data, the Multiple Use Safety and Efficacy Study (AE-97-08) showed that the combination provides meaningful relief to consumers under "real life conditions". In that trial, the combination was shown to improve the consumers' own assessment of their quality of sleep, and as shown in Figure 6, sleep duration was shown to correlate to quality of sleep. Taken

together, the data indicate that the combination of ibuprofen and diphenhydramine provides clinically meaningful relief of pain and sleeplessness to consumers, and it provides consumers with a more adequate duration of sleep relative to taking ibuprofen alone.

**Figure 6: Box and Whisker Plot of Duration of Sleep vs Sleep Quality - Study AE-97-08**



The box show the 75<sup>th</sup> and 25<sup>th</sup> percentiles. The width of the boxes are proportional to the sample size for each category of sleep quality. The line within the box is the 50<sup>th</sup> percentile (median) and the '+' is the mean. Top (bottom) lines represent the maximum (minimum) observation within 1.5 times the inter-quartile range (length of the box) from the top (bottom) of the box.

**IMPORTANCE OF SLEEP DURATION IN INSOMNIA MANAGEMENT**  
— , Ph.D.

Insomnia is defined as difficulty initiating, maintaining or non-restorative sleep associated with some type of negative daytime consequence. Insomnia problems are further characterized as transient (days to weeks) or chronic (months to years). The efficacy of sleep promoting agents (i.e. hypnotics) is defined by their ability induce sleep, maintain sleep or increase sleep duration. These efficacy parameters can be measured objectively with the use of sleep laboratory recordings (polysomnography), or based on subject/patient responses to question about their sleep. Sleep induction is measured by latency to persistent sleep (ten consecutive minutes of polysomnographically defined sleep) or a patient's response to how long it took him/her to fall asleep. Sleep maintenance is measured in the laboratory by wake time after sleep onset. There really is no subject/patient based response to measure pure sleep maintenance. Most commonly total sleep time is the measure used. Finally, sleep duration is measured in the laboratory by measuring total sleep time or sleep efficiency (total sleep time/time in bed). In non-laboratory trials, sleep duration is measured via subject estimates of sleep length. **Both the polysomnographic data as well as subject reports are seen as valid and important measures of efficacy.** Sleep laboratory data gets more at mechanism, as it is the basis of patient reports and is more precise. Subject reports get at clinical information. That is, they are the basis for patients deciding whether there is a resolution of the symptom they are trying to treat. **While patients with insomnia typically overestimate sleep latency and underestimate total sleep time, there is a high correlation between polysomnographic results and patient reports.** To date, no pharmacological agent has improved objective sleep measures without showing a parallel result for subjective measures. Sleep induction, as well as overall sleep duration parameters have been taken as indications of efficacy. **Sleep promoting agents have been approved which increased total sleep time but not sleep latency (temazepam) as well as ones which decreased sleep latency but did not increase total sleep time (zaleplon).**

It is difficult to decide which of the various outcome measures should be the most important. The decision as to which is the most important parameter depends on what is the morbidity of insomnia which we are trying to reverse or prevent with the use of a sleep promoting medication. **However, there are reasons to believe that total sleep time might be the most important.** First, the negative effects of sleep loss are most related to sleep duration. A loss of one to two hours total sleep time is associated with daytime impairment, as measured physiological measures of sleepiness (i.e. MSLT) as well psychomotor tests (e.g. divided attention, vigilance). Also, these deficits accumulate across successive nights of sleep loss. There is at least one study that shows that these impairments can be reversed with the use of a sleep promoting agent which increases total sleep time in a laboratory model of insomnia (i.e. reversal of sleep wake schedule). A second advantage of total sleep time is that it is the only measure which truly relates to sleep disturbances on a long term basis. Difficulty falling asleep may change across time to difficulty staying asleep. With increased pressure for sleep with multiple days of sleep onset problems, the patient may fall asleep rapidly, only to wake up later in the night with no net change in the amount of sleep obtained. Similarly, sleep maintenance problems may be resolved by simply restricting the time in bed. Again, when this has been tried (sleep restriction therapy) there has been no increase in sleep reported. Thus, while homeostatic and circadian factors may change the nature of the insomnia symptom, they do not effect total sleep time. In fact, research has shown that most patients with insomnia will experience a change in the nature of their insomnia symptom over time.

Effective insomnia management differs between long term problems (chronic insomnia) and occasional sleep problems. In chronic insomnia, the primary goal of therapy is to resolve symptoms, as the morbidity of the condition as well as the pathophysiology of the condition is not well understood. However, in the case of short term sleep problems (e.g. jet lag, acute pain) the morbidity of the condition is defined by two issues. First, the discomfort of the patient (patient reports) and second, the negative daytime consequences mediated by the restriction of

NDA 21-393 and 21-394  
June 11, 2002, Teleconference  
Page 20

sleep length. **Successful therapy is the resolution of the patient's symptoms and an increase in total sleep time.**

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/s/

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David Hilfiker  
7/18/02 04:44:50 PM  
CSO

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Ms. Mary Davis

**From:** Ms. Jane A. Dean, RN, MSN

**Fax:** 973-660-7187

**Fax:** 301-827-2531

**Phone:** 973-660-5825

**Phone:** 301-827-2090

**Pages:** (including cover page) 1

**Date:** 2 May 2002

**Re:** NDA 21-393

**Urgent**    **For Review**    **Please Comment**    **Please Reply**    **Please Recycle**

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● **Comments:** Dear Mary, it was really great to meet you at the DIA/FDA Workshop! Inserted below are some questions put forth from our OTC Division about the above referenced NDA:

During the conduct of 98-02, the secondary endpoint of sleep duration was changed to a primary endpoint based on looking at data from 98-01. This was done before the 98-02 study was unblinded. Please provide answers to the following questions on study 98-02.

The data from the case report forms was put into databases:

- Where were these databases housed (at Wyeth or was this resourced out)?
- Who had access to the information in the databases?
- How was the treatment group associated with the patient ID in the database during the data collection and up until the completion of the study?
- Did any of the individuals involved in the analysis of 98-01 also have access to the 98-02 database?
- Who had access to the randomization code of 98-02? Where was it stored?
- When was the decision made internally to change sleep duration to a co-primary endpoint?
- What considerations were taken into account when this decision was made?
- Were any blinded analysis done on the 98-02 data before September 20, 1999 or before you notified the FDA of the protocol amendment?

Thank you!

Jane A. Dean  
Project Manager

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/s/

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Jane Dean  
6/5/02 01:14:36 PM  
CSO

# MEETING MINUTES

**DATE:** 24 April 2002

**TIME:** 1630pm

**LOCATION:** Corp N300

**NDA 21-393 and NDA 21-394 Meeting Request Date:** 17 April 2002

**DRUG:** Ibuprofen 200mg and diphenhydramine 25mg

**SPONSOR/APPLICANT:** Wyeth Consumer Healthcare

## **FDA PARTICIPANTS: Office of Drug Evaluation V**

Jonca Bull, Office Director  
Charles Ganley, Division Director, OTC  
Lee Simon, Division Director, DAAODP  
Wiley Chambers, Deputy Division Director  
Stan Lin, Statistical Team Leader  
Stacey Welch, Project Manager  
Jane A. Dean, Project Manager

## **INDUSTRY PARTICIPANTS: Wyeth Consumer Healthcare**

Geraldine Doyle, PhD, Senior Director  
Roger Berlin, MD, President, Global Scientific Affairs  
Sharon Heddish, Vice President, Global Regulatory Affairs  
—, PhD, Consultant  
Stephen Cooper, DMD, PhD, Senior Vice President, Global Regulatory Affairs  
—, PhD, — (by telephone)

## **DISCUSSION:**

This meeting was initially proposed as a T-con. The sponsor chose to come in person for the meeting.

Although the original intent of the meeting was to advise the sponsor as to critical review issues with the application and to decide whether the application should be discussed at a June 20, 2001 advisory committee. In light of the current status of these review issues, the agency has decided that these issues did not warrant a discussion before an advisory committee at this time. Instead, the agency used this meeting to alert the sponsor to the review teams major concerns.

Because the application is under the final stages of review and the agency has no further information requests to make at this time, there would be no detailed discussion of the data during the meeting

The final regulatory action letter will be sent pending decision by the divisions on the appropriate action based on the reviews. It is unlikely to be an approval but it is unclear at this time whether it would be an approvable or not approval action. This will be discussed further internally. The sponsor will then have the option to request a meeting with the agency to discuss the action or to pursue further regulatory review through the dispute resolution process.

The objectives of the development plan were discussed. Based on a review of the minutes of the previous FDA/sponsor meetings, it was noted that the combination policy was

relevant to this drug product. The sponsor would be required to establish that the combination product was superior to diphenhydramine alone for pain and superior to ibuprofen alone for sleep.

It was also noted that the original protocol for study 98-01 and 98-02 listed the primary endpoint as a measurement of sleep latency. During development, an additional primary endpoint was added to study 98-02 based on results from 98-01 and the pilot study. The 98-02 study was already completed and reportedly not unblinded when the endpoint was added.

The following concerns were discussed with the sponsor:

1. Duration of sleep:

- The measurement for this endpoint was subjective and was obtained by asking the subject "How many hours did you sleep?" Additionally, subjects were awoken at 90 and 120 minutes after ingesting medication to evaluate pain;
- The measurement is not sufficiently accurate to be considered as a primary endpoint. The measurement was not accurately timed and it is unclear how the pain assessments at 90 and 120 minutes impacted the duration of sleep;
- If this measurement of sleep duration were proposed now as a primary endpoint in a new protocol, we would not accept it. There would need to be a more accurate way to measure duration of sleep;
- This endpoint would be fine as a secondary endpoint supportive of a significant primary endpoint;
- The Division of Neuropharmacology had concerns about the categorical nature of the endpoint, especially the category "< 5 hours". Most of the difference between the combination product and ibuprofen alone group was derived from the two category extremes ("< 5 hours", ">9 hours"). They don't know what impact that has on the results. They are generally accustomed to specific time being provided by the subject.

2. Study 98-02:

- The Division of Neuropharmacology had concerns about the robustness of the finding for sleep duration. The p = value was very dependent on the test done. They do not feel that this is a robust finding when this study is considered the pivotal study;

Duration of sleep (combination vs. ibuprofen)

Test	Approximate P value
ANOVA	.005
CMH (raw data method)	.01
CMH (generalized associations method)	.1

CMH = Cochran Mantel Haenszel

- For the primary endpoint of the cumulative percent asleep at 60 minutes (sleep latency), ibuprofen versus the combination yields a p = .09. Although not significant, it is close and clearly heading in the wrong direction. This finding is clearly inconsistent with the duration of sleep finding;
- For the pain primary endpoint, ibuprofen was significantly better than the combination. Although the difference numerically is not much, the fact that one can obtain a significant finding is troubling and raises issues about what the study is actually showing;
- There is an inconsistency in the results of the two primary sleep measurements. This raises questions as to what this study is actually showing.

The sponsor raised some questions about the statistical analysis, which were not answered because the purpose of the meeting was not to get into a detailed discussion of the data. The sponsor was assured that discussion on specific data could be addressed once the review process and action by the agency is finalized on the application. Questions about adequate sleep endpoints were not answered because Neuropharmacology was not involved in the meeting. The sponsor asked whether the agency statisticians could discuss some of the analyses before the letter was sent out. This was deferred and left for internal discussion.

**ACTION ITEMS:**

1. Determine whether the agency statisticians can have a dialogue with the sponsor statistician prior to the action letter.
2. Action letter once all discipline reviews are completed and internal discussion has taken place.

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/s/

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Lee Simon  
7/26/02 02:30:59 PM

**Wyeth Consumer Healthcare**  
5 Giralda Farms  
Madison, NJ 07940

**Mary H. Davis**  
Director, Regulatory Affairs

973 660 5825 tel  
davism@wyeth.com

**Wyeth**

March 19, 2002

**NDA 21-393**  
**Ibuprofen 200 mg/Diphenhydramine HCL 25 mg Liquigels (OTC)**

**Re: Update to ISS Study Information**

Lee S. Simon, MD, Director  
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTN: Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850

Dear Dr. Simon:

Please refer to NDA 21-393 for ibuprofen 200 mg/diphenhydramine HCL 25 mg Liquigels (OTC) sponsored by Wyeth Consumer Healthcare.

This submission serves as an update with minor corrections to the Integrated Summary of Safety (ISS) for NDA 21-393. Specifically, an error was detected in the programs that generated the SAS tables for the bioavailability studies in the ISS for NDA 21-393. The error was caused by inappropriate use of the "nodupkey" function while sorting the data sets by treatment and patient ID. The error caused undercounting of adverse events for relevant tables. The error has been corrected. Corrected safety tables (Tables B.D through B.H) have been replaced and the relevant text in the ISS revised.

Additionally, Table SC.2 "Number of Subjects with Adverse Experiences by Body System With Incidence Rate  $\geq$  2%" was re-run to match the title, and Table S.K "Number of Subjects with Adverse Experiences by Race" was re-run to fix treatment labels.

These errors produced no overall effect on the conclusions drawn in the ISS.

# Wyeth

This submission is an electronic submission, presented in an electronic format. The submission is contained on 1 CD-ROM, which is approximately 14 MB in size. A complete, corrected version of the ISS is included within this submission.

Please note that in the revised electronic version, only hyperlinks within the ISS are functional. Hyperlinks to other sections of the NDA are non-functional and marked "unresolved". Please use the bookmarks to navigate within the document.

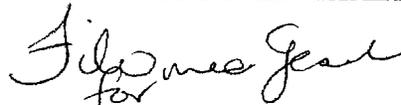
For ease of review, a paper desk copy that indicates the changes incorporated, is being provided to the Regulatory Project Manager, Ms. Jane Dean.

Wyeth Consumer Healthcare hereby certifies that this submission is virus-free and the following software used to check the files for viruses: McAfee VirusScan 4.1.60 by Network Associates, Inc., using virus definition file 4.0.4189 dated March 6, 2002.

If you have questions or comments regarding this information, please contact the undersigned at (973) 660-5825 or Ms. Filomena Gesek at (973) 660-6334.

Sincerely,

WYETH CONSUMER HEALTHCARE

A handwritten signature in cursive script that reads "Filomena Gesek" with a small "for" written below the name.

Mary H. Davis  
Director, Regulatory Affairs

Desk Copy: D. Bashaw, Pharm.D  
Biopharmaceutics Team Leader

J. Dean  
Regulatory Project Manager



**Mary H. Davis**  
Director, Regulatory Affairs

Whitehall-Robins  
Five Giralda Farms  
Madison, NJ 07940  
Telephone (973) 660-5825  
Fax (973) 660-7187  
E-mail address: davism@ahp.com

February 15, 2002

**NDA 21-393**  
**Advil® PM Liqui-Gels**  
**(Ibuprofen 200mg/diphenhydramine HCl 25 mg)**

**General Correspondence: Four-Month Safety Update**

Lee S. Simon, MD, Director  
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTN.: Document Control Room  
9201 Corporate Blvd.  
Rockville, MD 20850

Dear Dr. Simon:

Please refer to NDA 21-393 for Advil® PM Liqui-Gels, sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins"), a division of American Home Products Corporation. Specific reference is made to the Agency's fax of 1/7/02 confirming that only data for patients taking both active drugs concurrently be evaluated in the safety update.

Pursuant to 21 CFR 314.50(d)(5)(vi)(b), Whitehall-Robins herein submits its 4-Month Safety Update for the above-mentioned product. The sponsor has completed all clinical studies and submitted safety data from those studies in the original application for NDA 21,393. Therefore, this safety update consists of:

- update of AAPCC overdose data (year 2000)
- update of DAWN data (year 2000)
- reports to sponsor database since cut-off date (3/1/01)
- update of reports in AERS database
- a literature update.

Whitehall-Robins Healthcare  
General Correspondence: Four-Month Safety Update  
February 15, 2002

NDA 21-393  
Advil® PM Liquigels  
Ibuprofen/Diphenhydramine HCl Liquigels

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No changes to the proposed labeling are indicated based on the review of the poison control data and literature searched through December 31, 2001.

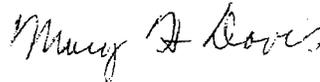
This submission is an electronic submission, presented entirely in an electronic format. The submission is contained on 1 CD-ROM, which is approximately 3.0 MB in size.

Whitehall-Robins hereby certifies that this submission is virus-free and the following software used to check the files for viruses: McAfee VirusScan 4.1.60 by Network Associates, Inc., using virus definition file 4.0.4184 dated 01/30/2002.

Should you have any questions, please contact the undersigned at (973) 660-5825 or Hugh McCain, Ph.D. at (973) 660-6031.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE



Mary H. Davis,  
Director, Regulatory Affairs



Mary H. Davis  
Director, Regulatory Affairs

Whitehall-Robins  
Five Giralda Farms  
Madison, NJ 07940  
Telephone (973) 660-5825  
Fax (973) 660-7187  
E-mail address: davism@ahp.com

January 11, 2002

**NDA 21-393**

**Ibuprofen 200 mg/diphenhydramine HCl 25 mg Liquigels (OTC)**

**General Correspondence: Response to FDA Request**

Lee S. Simon, MD, Director  
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTN: Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850

Dear Dr. Simon:

Please refer to NDA 21-393 for ibuprofen 200 mg/diphenhydramine HCl 25 mg Liquigels (OTC) sponsored by Whitehall-Robins Healthcare, a division of American Home Products Corporation. Specific reference is made to a fax from Barbara Gould of 7 January 2002.

As requested, included herewith, is the raw SAS output for Study AE-97-09 in both paper and electronic format.

Whitehall-Robins hereby certifies that this submission is virus-free and the following software was used to check for viruses: McAfee VirusScan 4.0.3 by Network Associates, Inc. using virus definition file 4.0.4178 dated 12/26/01.

If there are further questions regarding this information, please contact the undersigned at (973) 660-5825 or Filomena Gesek at (973) 660-6334.

Sincerely,  
WHITEHALL-ROBINS HEALTHCARE

Mary H. Davis  
Director, Regulatory Affairs



**Mary H. Davis**  
Director, Regulatory Affairs

Whitehall-Robins  
Five Giralda Farms  
Madison, NJ 07940  
Telephone (973) 660-5825  
Fax (973) 660-7187  
E-mail address: davism@ahp.com

January 7, 2002

**NDA 21-393**

**Ibuprofen 200 mg/diphenhydramine HCl 25 mg Liquigels (OTC)**

**General Correspondence: Response to FDA Request**

Lee S. Simon, MD, Director  
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTN: Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850

Dear Dr. Simon:

Please refer to NDA 21-393 for ibuprofen 200 mg/diphenhydramine HCl 25 mg Liquigels (OTC) sponsored by Whitehall-Robins Healthcare, a division of American Home Products Corporation. Specific reference is made to a fax from Barbara Gould of 18 December 2001.

As requested, this submission includes a by-patient, derived efficacy dataset (SAS transport) including all randomized patients for Study AE 97-08. The variables specifically requested (patient number, treatment code, center codes, patient demographics and baseline characteristics, patient disposition, primary and secondary efficacy variables) have been included.

Whitehall-Robins hereby certifies that this submission is virus-free and the following software was used to check for viruses: McAfee VirusScan 4.0.3 by Network Associates, Inc. using virus definition file 4.0.4178 dated 12/26/01.

Whitehall-Robins Healthcare  
Statistical Information Request  
January 7, 2002

NDA 21-393  
Advil PM Liquigels  
Ibuprofen/Diphenhydramine HCl Liquigels

If you have questions regarding this information, please contact the undersigned at (973) 660-5825 or Ms. Filomena Gesek at (973) 660-6334.

Sincerely,  
WHITEHALL-ROBINS HEALTHCARE

A handwritten signature in cursive script that reads "Mary H. Davis".

Mary H. Davis  
Director, Regulatory Affairs

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Mary Davis **From:** Barbara Gould

**Fax:** 973-660-7187 **Fax:** 301-827-2531

**Phone:** 973 660-5825 **Phone:** 301-827-2019

**Pages:** 1 (including cover) **Date:** 07-January-02

**Re:** NDA 21-393 Biopharm Information Request

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● **Comments:**

Please provide the raw SAS output for Study AE-97-09 in N21-393 Advil PM Liquigels. Raw SAS outputs were included for only two studies (see page 6-47-97 in the submission).

If you have any questions, please call.

Thanks,

BJ Gould

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/s/

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Barbara Gould  
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# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Mary Davis **From:** Barbara Gould

**Fax:** 973-660-7187 **Fax:** 301-827-2531

**Phone:** 973 660-5825 **Phone:** 301-827-2019

**Pages:** 1 (including cover) **Date:** 04-December-01

**Re:** NDA 21-393 Statistical Information Request

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● **Comments:**

Please provide for review for NDA 21-393, a by-patient data set (SAS transport) including all randomized patients for Study AE-97-08. In the data set, please include patient number, treatment code, center codes, patient demographics and baseline characteristics, patient disposition (time to withdrawal (study duration) and type of withdrawal), primary and secondary efficacy variables (time to event and censoring information should be included for survival type of analysis). If a study is multinational, please also include patient's nationality in the dataset. Please provide documentation if formats are used.

If you have any questions, please call.

Thanks,

BJ Gould

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/s/

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Barbara Gould  
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# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Mary Davis **From:** Barbara Gould

**Fax:** 973-660-7187 **Fax:** 301-827-2531

**Phone:** 973 660-5825 **Phone:** 301-827-2019

**Pages:** 1 (including cover) **Date:** 04-December-01

**Re:** NDA 21-393 Statistical Information Request

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● **Comments:**

Please refer to your fax dated December 14, 2001 for the safety update for NDA 21-393 in which you proposed the following:

- Any reports received since the cut-off date in the sponsor's own spontaneous adverse event database describing patients who concurrently took both active drugs
- When available from AAPCC, an update of the overdose data involving patients who concurrently took both active drugs
- Any new literature reports involving patients who concurrently took both active drugs

Your proposal for the safety update is acceptable.

If you have any questions, please call.

Thanks,

BJ Gould

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/s/

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Barbara Gould  
1/4/02 05:54:59 PM  
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# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Mary Davis **From:** Barbara Gould

**Fax:** 973-660-7187 **Fax:** 301-827-2531

**Phone:** 973 660-5825 **Phone:** 301-827-2019

**Pages:** 2 (including cover) **Date:** 29-November-01

**Re:** IND → Update of PreNDA Telecon Attendees

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● **Comments:**

Hi Mary,

Listed below are the attendees from today's telecon.

**FDA PARTICIPANTS:**

Jonca C. Bull, MD  
Lee S. Simon, MD  
Christina Fang, MD  
Abi Adebawale, Ph.D.  
Stan Lin, Ph.D.  
Jyoti Zalkikar, Ph.D.  
Maria Rivera, Ph.D.  
Sue Ching Lin, M.S., R.Ph.  
Barbara Gould

Charles Ganley, MD  
Daiva Shetty, MD  
Marina Chang, R.Ph.  
Michael Benson, R.Ph., JD

**Division of Anti-Inflammatory, Analgesic & Ophthalmic Drug Products**

Deputy Director, Acting Director, Office of Drug Evaluation V  
Division Director  
Medical Reviewer  
Biopharmaceutics Reviewer  
Biostatistics Team Leader  
Biostatistics Reviewer  
Pharm/Tox Reviewer  
Chemistry Reviewer  
Project Manager

**Division of Over-the-Counter Drug Products**

Division Director  
Medical Reviewer  
Interdisciplinary Science Team Leader  
Regulatory Review Pharmacist

IND

29-Nov-01 Page 2

Elaine Abraham  
Ansley Holland

Project Manager  
Pharmacy Student  
**Division of Pulmonary Drug Products**  
Medical Reviewer

Charles E. Lee, MD

If you have any questions, please call.

Thanks,

BJ Gould

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/s/

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Barbara Gould  
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**Mary H. Davis**  
Director, Regulatory Affairs

Whitehall-Robins  
Five Giralda Farms  
Madison, NJ 07940  
Telephone (973) 660-5825  
Fax (973) 660-7187  
E-mail address: davism@ahp.com

October 16, 2001

**NDA 21-393**  
**Advil PM Liqui-Gels**  
**(Ibuprofen 200 mg / Diphenhydramine HCL 25 mg)**

**New Drug Application**

Jonca Bull, M.D., Director  
Division of Anti-Inflammatory, Analgesic,  
And Ophthalmic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTENTION: Document Control Room  
9201 Corporate Blvd  
Rockville, MD 20850

Dear Dr. Bull

Submitted herewith is a New Drug Application, sponsored by Whitehall-Robins Healthcare, a division of American Home Products Corporation, for a nighttime pain reliever/sleep aid, Advil PM. This NDA is submitted in support of a liquigel dosage form containing ibuprofen 200 mg and diphenhydramine hydrochloride 25 mg per liquid-filled capsule. Whitehall-Robins is simultaneously filing a New Drug Application for a caplet dosage form of Advil PM containing ibuprofen 200 mg and diphenhydramine citrate 38 mg per caplet (NDA 21-394). Support for the pre-clinical and clinical sections of the caplet application are made by cross-reference to this NDA. Data to support the bioequivalence of the caplet dosage form is included in that NDA.

This submission is an electronic submission. The entire submission is presented in an electronic format. The submission is contained on 2 CD-ROMs, which is approximately 900MB in size.

Whitehall-Robins hereby certifies that this submission is virus-free and the following software was used to check the files for viruses: McAfee VirusScan 4 0.3 by Network Associates, Inc. using virus definition file 4.0.4164 dated 10/3/2001.

Whitehall-Robins Healthcare  
Original NDA  
October 16, 2001

NDA 21-393  
Advil PM Liquegels  
Ibuprofen/Diphenhydramine citrate Liquegels

Whitehall-Robins hereby also certifies that a copy of this submission has been forwarded to the FDA District Offices in North Brunswick, NJ and Baltimore, MD. If you have any questions or comments regarding this information, please contact the undersigned at (973) 660-5825 [fax (973) 660-7187] or Hugh McCain at (973) 660-6031.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE



Mary H. Davis  
Director, Regulatory Affairs

### 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).

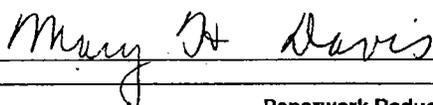
Please mark the applicable checkbox.

- 7
- (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		

- (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)).

- U
- (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 Mary Davis	TITLE Director, Regulatory Affairs
FIRM/ORGANIZATION Whitchall-Robins Healthcare	
SIGNATURE 	DATE 10/16/2001

#### 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  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

D

3 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297  
Expiration Date: 04-30-01

# USER FEE COVER SHEET

*See Instructions on Reverse Side Before Completing This Form*

1. APPLICANT'S NAME AND ADDRESS Vernitehall Robins Healthcare 5 Giralda Farms Madison, New Jersey 07940		3. PRODUCT NAME Advil PM Liquegels
2. TELEPHONE NUMBER (Include Area Code) ( 973 ) 660-5825		4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? 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: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE I.D. NUMBER 4158		

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

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 <i>(Self Explanatory)</i>	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <i>(See item 7, reverse side before checking box.)</i>
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <i>(See item 7, reverse side before checking box.)</i>	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act <i>(See item 7, reverse side before checking box.)</i>
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY <i>(Self Explanatory)</i>	

**FOR BIOLOGICAL PRODUCTS ONLY**

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  YES  NO  
*(See reverse side if answered YES)*

***A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.***

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:

DHHS, Reports Clearance Officer  
Paperwork Reduction Project (0910-0297)  
Hubert H. Humphrey Building, Room 531-H  
200 Independence Avenue, S.W.  
Washington, DC 20201

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.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Sharon Heddish</i>	TITLE <i>VP Reg Affairs</i> CONFIDENTIAL	DATE <i>8-20-01</i> 18-447-1
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WHITEHALL-ROBINS

P.O. BOX 26609  
RICHMOND, VIRGINIA 23261-6609

REMITTANCE  
STATEMENT

DATE	CHECK NO.
08/13/01	865474
NUAP	133942

DATE	INVOICE / CREDIT MEMO	TYPE	DESCRIPTION	GROSS	DISCOUNT	NET
01	080471 ADVIL PM LIQUID		080801 0021 GUSER FEE 4158	30964700	00	30964700
			NDAZI-595 PDA PO BOX 360909			
<b>TOTAL</b>				<b>30964700</b>	<b>000</b>	<b>30964700</b>

THE ACCOMPANYING CHECK IS  
IN PAYMENT OF THE ITEMS LISTED ABOVE



P.O. BOX 26609  
RICHMOND, VIRGINIA 23261-6609

62-26 2607-09  
311

CHECK NO. 865474

THIS CHECK CONTAINS MULTIPLE FRAUD DETERRENT SECURITY FEATURES

865474

PAY

THREE HUNDRED NINE THOUSAND SIX HUNDRED FORTY-SEVEN DOLLARS AND NO CENTS

TO THE ORDER OF

FOOD & DRUG ADMINISTRATION  
P O BOX 360909  
PITTSBURGH PA 15251-6909

DATE

08/13/01 \*\*\*\*\*309,647.00

CHECK AMOUNT

*Kristen Lomer*  
*J. B. Leatherbury*  
WHITEHALL-ROBINS • VOID AFTER 180 DAYS

CHASE MANHATTAN BANK DELAWARE • WILMINGTON, DELAWARE 19801

⑈00865474⑈ ⑆031100267⑆ 6301426072 509⑈



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 44,767/IND 56,521

Whitehall-Robins  
Attn: Mary H. Davis  
Director, Regulatory Affairs  
Five Giralda Farms  
Madison, NJ 07940

Dear Ms. Davis:

Reference is made to your correspondence dated August 30, 2001, requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for ibuprofen 200 mg/diphenhydramine HCl 25 mg liquigel and ibuprofen 200 mg/diphenhydramine citrate 38 mg tablets for relief of occasional sleeplessness when associated with                      minor aches and pain, for the pediatric population. The age ranges for the granted waiver are 0 to less than 12 of age.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have questions, please contact Barbara Gould, Regulatory Project Manager, at 301 827-2090.

Sincerely,

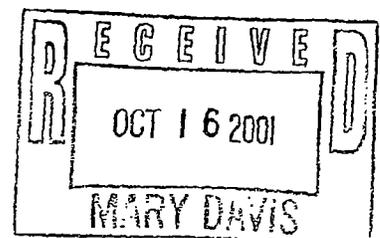
*{See appended electronic signature page}*

Jonca C. Bull, M.D.  
Deputy Director, and Acting Director,  
Office of Drug Evaluation V  
Acting Division Director  
Division of Anti-Inflammatory, Analgesic, &  
Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
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.**  
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/s/

-----  
Jonca Bull  
10/11/01 08:37:48 AM





Mary H. Davis  
Director, Regulatory Affairs

Whitehall-Robins  
Five Giralda Farms  
Madison, NJ 07940  
Telephone (973) 660-5825  
Fax (973) 660-7187  
E-mail address: davism@ahp.com

August 30, 2001

IND 56,521  
Ibuprofen 200 mg/Diphenhydramine HCl 25 mg Liquigels (OTC)  
Serial No. 037

**General Correspondence: Request for Waiver of the Pediatric Study Requirements**

Jonca Bull, MD, Acting Director  
Division of Analgesic and Anti-inflammatory Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
Attn: Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850

Dear Dr. Bull:

Pursuant to 21 CFR 314.90 (a), Whitehall-Robins Healthcare, ("Whitehall-Robins"), a division of American Home Products Corporation, is requesting a full waiver of the requirements for pediatric assessment of Ibuprofen 200 mg/Diphenhydramine 25 mg Liquigels (OTC). Per the Guidance for Industry entitled "Recommendations for Complying With the Pediatric Rule (21 CFR 314.55 (a) and 601.27 (a))", attached is the request for Waiver of Pediatric Studies.

Please note that the following NDA number has been assigned for this product: 21-393.

If there are any questions or comments regarding this submission, please contact the undersigned at (973) 660-5825 or Lisa Tran at (973) 660-6693.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Mary H. Davis  
Director, Regulatory Affairs

# TELECON MINUTES

**TELECON DATE:** December 01, 2000 **TIME:** 11:30 a.m. **LOCATION:** Corp S300

**IND #:** 56,521

**Telecon Request Submission Date:** August 16, 2000

**Briefing Document Submission Date:** October 27, 2000

**DRUG:** Ibuprofen 200 mg and Diphenhydramine HCl 25 mg Liquigels

**SPONSOR/APPLICANT:** Whitehall Robins

**TYPE of TELECON:** PreNDA

**FDA PARTICIPANTS:**

Robert J. DeLap, M.D.  
Larry Goldkind, M.D.  
Christina Fang, M.D.  
Robert Osterberg, Ph.D.  
Conrad Chen, Ph.D.  
Maria Rivera, Ph.D.  
Dennis Bashaw, Pharm.D.  
Abi Adebawale, Ph.D.  
Stan Lin, Ph.D.  
Laura Hong Lu, Ph.D.  
Sandra Folkendt  
Barbara Gould

**Division of Anti-Inflammatory, Analgesics, and Ophthalmic Drug Products**

Director, Office of Drug Evaluation V  
Medical Officer Team Leader  
Medical Reviewer  
Acting Pharmacology Team Leader  
Pharmacology Reviewer  
Pharmacology Reviewer  
Biopharmaceutics Team Leader  
Biopharmaceutics Reviewer  
Statistical Team Leader  
Statistical Reviewer  
Project Manager  
Project Manager

Linda Katz, M.D.

Linda Hu, M.D.

Marina Chang, R.Ph.

Ida Yoder

Michael Benson, R.Ph. J.D.

Babette Merritt

**Division of Over-the-Counter Drug Products**

Deputy Director  
Medical Reviewer  
Interdisciplinary Scientist Team Leader  
Interdisciplinary Scientist  
Regulatory Reviewer-Pharmacist  
Project Manager

Paul Andreason, M.D.

**Division of Neuropharmacological Drug Products**

Medical Reviewer

**INDUSTRY PARTICIPANTS:**

Roger Berlin, M.D.

Stephen Cooper, DMD, Ph.D.,

Sharon Heddish

Joel Waksman, Ph.D.

Geraldine Doyle, Ph.D.

Mary Davis

Lisa Tran

Elizabeth Ashraf

Hulon McCain

Shymalie Jayawardena

Robin Weitz

**Whitehall Robins Healthcare**

President, Global Scientific Affairs

Senior Vice President, Global Clinical and Medical Affairs

Vice President, Regulatory Affairs Worldwide

Senior Director, Biostatistics and Data Management

Senior Director, Clinical Affairs

Director, Regulatory Affairs

Manager, Regulatory Affairs

Senior Director, Medical Communications

Director, Regulatory Affairs, Toxicology

Senior Statistician, Biostatistics

Associate Director, Regulatory Affairs, Submissions and Archives

**TELECON OBJECTIVES:**

The purpose of this teleconference is to obtain the Division's agreement regarding the proposed contents for each section of the NDA and identify any issues or concerns that need to be specifically addressed in the application.

**BACKGROUND INFORMATION:**

Reference is made to Whitehall Robins IND 56,521 submitted for a non-prescription analgesic/sleep-aid combination product containing ibuprofen and diphenhydramine. Whitehall plans to submit New Drug Application for the above referenced product in November 2001.

Attendees from FDA and Whitehall Robins were introduced. Prior to the teleconference draft responses to questions submitted in the briefing document were faxed to the company. Whitehall had reviewed and agreed that the response to the questions was acceptable; however, clarification was needed for some of the responses.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

The responses to the following questions pertain to the format of the proposed NDA. These responses do not evaluate whether the data (as provided in the briefing package) are or are not adequate to support filing of an NDA. The adequacy of the data to support an NDA will be a review issue.

**1. Item 5: Non-Clinical Pharmacology/Toxicology**

- Does the Agency have comments on the proposed pharmacology/toxicology section?

FDA Response:

A summary evaluation of non-clinical pharmacological and toxicology information from public literature and other available sources for the detection of possible additive, synergistic or antagonistic effects of the drug combination should be made.

**2. Item 6: Human Pharmacokinetics and Bioavailability**

- Is the proposal for this section acceptable to the Agency?

FDA Response:

Yes.

- Are there any specific concerns you would like addressed in this section?

FDA Response:

No, but the sponsor should provide dissolution data in the package.

**3. Item 8d: Clinical Data---Controlled Studies/Statistical Analyses**

- Are the statistical methods of analysis acceptable?

FDA Response:

Data should be analyzed in accordance with the prespecified analysis plans. Justifications should be provided in the NDA for significant changes or additions to the analysis plans.

For sleep duration, the Agency would like to sponsor to provide an additional analysis, as a way of further examining the robustness of the study findings. In this analysis, each category (0-5) of sleep duration should be identified as the middle value at the original hourly scale, i.e.,

the category 0 should be 2.5  $((0+5)/2)$  hours;

the category 1 should be 5.5  $((5+6)/2)$  hours;

the category 2 should be 6.5  $((6+7)/2)$  hours;

the category 3 should be 7.5  $((7+8)/2)$  hours;

the category 4 should be 8.5  $((8+9)/2)$  hours;

the category 5 should be 9.5 (a rough estimate) hours.

ANOVA method can be applied with other pre-specified factors as covariates.

Although this additional analysis will not provide an accurate result for sleep duration, it can serve as a secondary analysis to assess the robustness of the prespecified analysis.

WRH Response:

WRH agreed to submit additional analysis.

- Is the presentation of results in the data tables acceptable?

FDA Response:

The efficacy data table should be labeled more clearly to show the variables being measured and in what units (e.g. total time slept or change from baseline TTS). Attached is a sample template that was provided previously at a pre-NDA meeting.

**4. Item 8f: Clinical Data—Other Studies and Information**

- Does the agency agree with the inclusion of the four proposed studies in this section?

FDA Response:

The four studies are appropriately included in this section.

- In this section, is it acceptable to include synopses of the study results in place of a full report?

FDA Response:

Yes, however a full report should be provided for Study CRD 85-31. This may be the only full factorial study in the development program that provides evidence that the combination is more effective than either of the components with regard to sleep parameters. While the dose ratio of ibuprofen and diphenhydramine studied in 85-31 differs from the dose ratio in the products proposed for marketing, that study may still provide useful information in support of the application. Thus, a full study report of study CRD 85-31 is warranted for the NDA submission.

- Is the plan to address AEs in the ISS acceptable?

FDA Response:

No changes are requested at this time, however, needs for additional analyses and/or presentations of AEs may be identified during review of an NDA. The Agency reemphasizes collecting all information from all potential data sources for spontaneous adverse event reporting.

**5. Item 8h: Integrated Summary of Effectiveness of (ISE) Data**

- Does the Agency agree with the proposed inter-study comparisons?

FDA Response:

This is a relatively creative way of looking at gender and race effects; however, whether the analysis will be useful in the end is a matter of review. The Agency strongly recommends a discussion concerning the targeted population for which this product will be marketed. (Please refer to Question #2 of the July 1, 1999 meeting minutes with the sponsor.)

FDA asked Whitehall Robins to do subgroup analysis by age. The population appears younger than at the last meeting. More information is needed on the different age groups; particularly information on the elderly population is more important.

- Does the Agency agree with the proposal for pooling the oral surgery studies?

FDA Response:

Pooled results can be provided as additional information.

- Does the Agency agree with the proposed assessment of demographic/drug, disease/drug, and drug/drug interactions?

FDA Response:

These are mostly safety issues and this type of pooling is routinely done in regards to the sleep duration studies, if the studies are appropriately similar with respect to design, duration and demographic makeup. This should be declared upfront for the reviewer.

As previously expressed, the Agency has particular concern for safety of this product in the elderly. It is acceptable for Whitehall Robins to draw on the other sources of information to help address these issues. Studies should be analyzed as proposed in prespecified plan. Justification for pooling of studies is required. If additional analyses are submitted the justification should be provided.

- Is the presentation of results in the sample data tables acceptable?

FDA Response:

There are no additional requests at this time. This is a review issue. See item #3.

**6. Item 8h: Integrated Summary of Safety Information**

- Is the proposed pooling of the studies acceptable?

FDA Response:

On face value the pooling appears appropriate, but this is a question that is most appropriately answered during the review process.

- Are there other sub-group analyses required/recommended?

FDA Response:

The need for careful examination of age, gender, race and other relevant demographics is reiterated.

- Is the presentation of summaries in the attached tables acceptable?

FDA Response:

There are no additional requests at this time. This is a review issue. See item #3.

- We are not planning to include AE data from currently marketed analgesic-sleep aid products (e.g., Tylenol PM). Is this acceptable?

FDA Response:

Yes, but include AE data from all of the clinical trial arms, as well as any relevant safety information from abroad on ibuprofen/diphenhydramine combination products.

WHR Response:

Whitehall agreed to collect all AE data on the use of these two drugs together including information from the literature.

## 7. Electronic Submission

- Does the Agency have comments on this section?

FDA Response:

The sponsor should submit a by patient (one record per patient) ITT efficacy data set for each of the pivotal efficacy studies. Each data set should include patient number, treatment code, investigator, demographic variables, reason for terminating study, all primary and secondary efficacy variables at each time point. The formats for characteristic variables such as investigator site, treatment, gender, race, and reason for terminating study should be provided. For OTC safety study, safety variables should be included as well.

- Does the Agency agree with the contents of the paper review copy?

FDA Response:

Please refer to the guidance documents for electronic submission on the CDER web site at the following address: <http://www.fda.gov/cder/guidance/index.htm>.

- How many review copies will FDA require?

FDA Response:

Please refer to the guidance documents for electronic submission on the CDER web site at the following address: <http://www.fda.gov/cder/guidance/index.htm>. Also include a copy for Over the Counter Drug Products and provide a copy of the labeling and tables in Word 97.

**8. General**

- References will be available upon request but will not be included for Items 5, 6, 8d, 8f, 8g, and 8h. Is this acceptable?

FDA Response:

No. If the sponsor cites literature for the above listed items, then copies of the cited documents need to be provided.

For Item 5: Provide information on mutagenicity and carcinogenicity for ibuprofen, diphenhydramine and the combination drug if available.

**Additional comments**

1. Usage study will be analyzing efficacy dose from the first day of administration for patients with both pain and sleeplessness. All patients should be included in the ITT analysis.
2. There are several hypothesis listed in the submission. Multiple comparison could be an issue.

**ACTION ITEMS:**

1. Project Manager will convey minutes within 30 days.

Barbara Gould 01-04-01  
Barbara Gould  
Project Manager

Concurrence Chair: Jonca Bull for Dr. DeLap  
Robert DeLap, M.D.  
Director, Office of Drug Evaluation V

IND# 56,521 Whitehall Robins  
Mtg. Date: December 01, 2000 PreNDA Meeting  
Page 8

cc: IND# 56,521  
HFD-550/Div File  
HFD-550/RDelap/  
HFD-550/LGoldkind/CFang/  
HFD-550/ROsterberg/CoChen/MRivera/  
HFD-550/DBashaw/AAdebowale/  
HFD-550/StLin/LHu/  
HFD-550/LVaccari/  
HFD-550/SCook/BGould  
HFD-560/LKatz/  
HFD-560/LHu/

Initialed by:

RDelap/01-08-01  
LGoldkind/01-04-01 no change  
CFang/No Response Rec'd  
ROsterberg/01-04-01 no change  
CoChen/No Response Rec'd  
DBashaw/01-04-01 no change  
AAdebowale/12-20-00  
StLin/01-04-01 no change  
LuHo/12-20-00  
LVaccari/  
LKatz/01-04-00 no change  
LHu/12-19-00

**TELECON MINUTES**

Faxed: January 9, 2001

/s/

-----  
Jonca Bull

1/22/01 04:31:49 PM

**APPEARS THIS WAY  
ON ORIGINAL**

## TELECONFERENCE MINUTES

IND: 56,521

DATE: 5/12/00

PRODUCT NAME: Ibuprofen/Diphenhydramine HCl Liqui-Gels, Advil PM

SPONSOR: Whitehall-Robins

### Whitehall-Robins Healthcare:

Stephen Cooper, DMD, Ph.D.	V. P., Clinical Science and Medical Affairs
Mary Davis	Associate Director, Regulatory Affairs
Geraldine Doyle, Ph.D.	Director, Clinical Affairs
Sharon Heddish	Vice President, Regulatory Affairs Worldwide
Joel Waksman, Ph.D.	Senior Director of Biostatistics
Lisa Tran, M.Sc.	Regulatory Affairs

### FDA:

Robert DeLap, M.D., Ph.D.	Director, ODE V
Karen Mithun, M.D.	Director, HFD-550
Charles Ganley, M.D.	Director, OTC Drug Products
Linda Hu, M.D.	Medical Officer
Sandra N. Cook	Project Manager
Stan Lin, Ph.D.	Team Leader, Statistics
Abi Adebowale, Ph.D.	Biopharmaceutics Reviewer
E. Dennis Bashaw, Pharm.D.	Team Leader, Biopharmaceutics
Mona Zarifa, Ph.D.	Acting Team Leader, Chemistry
Mary Jane Walling	Associate Director for Regulatory Policy, ODE V
Michael Benson, R.Ph.	Regulatory Review Pharmacologist
Marina Chang, R.Ph.	Interdisciplinary Scientist
Tom Parmelee, Pharm.D.	Project Manager

**SUBJECT:** Whitehall-Robins (W-R) requested a teleconference to discuss the safety protocol for their ibuprofen/diphenhydramine HCl liquigels.

### Question 1

**Does the Agency agree with the revised inclusion/exclusion criteria?**

- FDA recommends incorporating self-selection in this trial, as much as possible.
- Please clarify whether the trial is double-blind or double-dummy
- Please clarify in the protocol reasons why an investigator can "kick-out" a patient
- Should the investigator disallow patients who select incorrectly? Yes, for patients at risk for serious adverse events (e.g., anaphylaxis), otherwise no.

### Question 2

**Can the assessment of efficacy be deleted as an objective of the protocol, and can subjects be allowed to begin dosing the first evening subsequent to enrollment (regardless of whether or not they are experiencing any symptoms of sleeplessness and pain)?**

FDA recommended that Whitehall look at efficacy with the first dose. FDA also stated that an inconclusive finding in such an analysis would not be viewed as detracting from other efficacy findings in a NDA package.

**Question 3**

**Does the Agency agree with the proposed assessments of sleep latency, duration, and quality of sleep, as well as pain relief?**

The proposal appears acceptable. FDA recommends using a Visual Analog Scale for sleep quality. The proposed sleep duration scale could be problematic. Ask subjects to record the number of hours of sleep.

The proposed pain relief scale is acceptable.

**Question 4**

**Can the caplet be used as the final market formulation based solely on a successful bridging bioequivalence study? Will this be sufficient for filing an NDA for the caplet formulation instead of the liquigel formulation?**

The proposal will be sufficient for filing a NDA provided that bioequivalence is demonstrated with Cmax and AUC.

**Question 5**

**Does the Agency have any concerns that the liquigel formulation contains diphenhydramine hydrochloride 25 mg (per liquigel) and the caplet contains diphenhydramine citrate 38 mg (per caplet)?**

Whitehall will need separate NDAs if they want to market both formulations.

**Question 6**

**Since this is a medication exclusively used at bedtime, is a fed arm relevant in the bioequivalence study?**

A food study, while useful, would not be required for this product.

**Question 7**

**Assuming a fed arm is required, we are proposing that 12 of the 36 subjects receive the caplet fed treatment? Is this acceptable?**

Should the sponsor choose to do such a study, the proposed dosing scheme with meals is acceptable.

**Question 8**

**For the statistical comparison of caplets fasted versus caplets fed, we propose to use the data from only the 12 subjects exposed to both of these formulations. Is this acceptable?**

The sponsor is directed to the draft FDA Food Effect Guidance for direction on the evaluation and interpretation of these studies.

/s/

-----  
Sandra Folkendt  
1/22/01 03:25:56 PM  
CSO

Robert DeLap  
1/24/01 04:45:55 PM  
MEDICAL OFFICER

## MEETING MINUTES

**MEETING DATE:** February 24, 2000  
Time: 3-4:40 pm  
Location: Corp S400

**IND 56,521**

Date Meeting Requested: 12-17-99  
Briefing Doc submitted: 12-17-99

**DRUG:** Advil PM (ibuprofen 200 mg/diphenhydramine HCl 25 mg liguigels)

**SPONSOR:** Whitehall-Robins Healthcare

**TYPE OF MEETING:** PreNDA Meeting

The purpose of the meeting is to discuss the results of the efficacy portion of the clinical development program for Advil PM.

Indication: For the relief of occasional sleeplessness when associated with — minor aches and pains.

### FDA ATTENDEES:

Robert DeLap, MD, PhD, Director, Office of Drug Evaluation V  
Karen Midthun, MD, Director, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (DAAODP)  
Christina Fang, MD, Medical Officer (DAAODP)  
Conrad Chen, PhD, Pharmacologist (DAAODP)  
Mona Zarifa, PhD, Chemist, Acting Team Leader (DAAODP)  
Leslie Vaccari, Acting, Chief Project Management Staff (DAAODP)  
Paul Andreason, MD, Medical Officer, Division of Neuropharmacological Drug Products  
Dennis Bashaw, PharmD, Clinical Pharmacology and Biopharmaceutics  
Abi Adebowale, PhD, Reviewer Clinical Pharmacology and Biopharmaceutics  
Laura Lu, PhD, Statistician, (DAAODP)  
Charles Ganley, MD, Director, Division of Over-the-Counter Drug Products (DOTCDP)  
Linda M. Katz, MD, MPH, Deputy Director, DOTCDP  
Rosemarie Neuner, MD, MPH, Medical Officer, DOTCDP  
Michael Benson, RPh, Regulatory Review Pharmacologist, DOTCDP  
Linda Hu, MD, Medical Officer, DOTCDP  
Marina Chang, RPh, Regulatory Review Pharmacologist, DOTCDP  
Tom Parmalee, Project Manager, DOTCDP  
Debbie Lumpkins, Team Leader, DOTCDP  
Kerry Rothschild, Project Manager, DOTCDP

### INDUSTRY ATTENDEES:

Roger Berlin, M.D., President Global Scientific Affairs  
Stephen Cooper, DMD, Ph.D., Vice President, Clinical and Medical Affairs  
Joel Waksman, Ph.D., Senior Director, Biostatistics  
Geraldine Doyle, Ph.D., Senior Director, Clinical Affairs  
Sharon Heddish, Vice President, Regulatory Affairs Worldwide  
Mary Davis, Director, Regulatory Affairs  
—, Consultant —

**PRESENTATION:** A ten-minute presentation was made by Whitehall-Robins Healthcare following introductions. Refer to the attached copies of the overheads.

**BACKGROUND:**

The sponsor has completed three factorial studies in a modified oral surgery pain model (1 pilot full factorial and 2 pivotal partial factorials) evaluating the efficacy of the combination versus ibuprofen alone. One dose-response study and two studies in tension headache (1 pilot and 1 pivotal) have also been completed. A 10-day multiple-dose study is planned to begin enrollment in April, 2000 in approximately 900 individuals who have a history of experiencing sleeplessness associated with headaches or any type or minor aches and pains. This study is designed to compare the safety and efficacy of 1 Advil PM Liquigel, 2 Advil PM Liquigels, 2 Tylenol PM caplets and placebo for 10 consecutive days.

**QUESTIONS FOR DISCUSSION SUBMITTED BY WHITEHALL-ROBINS**

**1. Whitehall Question:**

*Two pivotal partial studies were conducted in the modified oral surgery model. Duration was a primary endpoint in one of the pivotal studies and a secondary endpoint in the other. If the Agency review results in a similar interpretation of the data, are increased duration and quality of sleep acceptable outcomes to obtain approval of the combination?*

Following a preliminary comment by the FDA, Whitehall provided further explanation relating to the above question. Sleep latency, duration of sleep and sleep quality are the predetermined efficacy parameters for sleep evaluation. Sleep latency, defined as the cumulative proportion of patients asleep at 60 minutes, and decrease in pain are primary endpoints. Duration of sleep was designated as a secondary endpoint for the pilot and first factorial study. Following these two studies, Whitehall observed that the advantage of the combination was the increase in the duration of sleep. As a result, duration of sleep was specified as a primary endpoint in the subsequent pivotal study. Whitehall emphasized that the increase in the duration of sleep is the more important parameter in the overall sleep evaluation and urged the FDA to consider this.

**FDA Response:**

It was acknowledged that Whitehall believes that diphenhydramine significantly contributes to the combination (ibuprofen and diphenhydramine) as a pain medication and sleep-aide. The question remains for the FDA to address whether the benefit of diphenhydramine by extending sleep duration is adequate to demonstrate clinical benefit of the combination.

During upcoming FDA consideration of this product, close appraisal will be needed of what the consumer may expect from this type of OTC product. For example, whether or not someone would take a sleep-aide for sleeplessness associated with pain or simply take a pain medication to resolve sleeplessness must be considered.

Whitehall has consistently communicated with the FDA during the development of this combination product. The FDA anticipates the clinical section of the application may be adequate for submission based on the preliminary information provided today.

FDA does have concern regarding the primary endpoint because the data summarized in the briefing document does not support the efficacy for sleep latency in all studies. However, any conclusion regarding efficacy is a review issue and as such will be evaluated during the

review of the application. In addition, the significance of the sleep duration and quality of sleep data relative to the outcome of the review of this application can not be predicted at this time.

2. **Whitehall Question:**

*Is the magnitude of difference seen in the dose response study (03) an indicator that 2 liquisolids are the appropriate recommended dose for the combination?*

**FDA Response:**

This is a review issue.

3. **Whitehall Question:**

*We believe that we have addressed all of the concerns regarding a 10-day multiple use study. Does the Agency concur?*

**FDA Response:**

- a) Exclusion from entering the study should be accomplished by patient self-selection as a result of following the labeling instructions and not by an investigator.
- b) There should be 300 patients in each arm in order that adverse events occurring over the 1% level can be detected.
- c) The study design includes efficacy parameters that remain a concern. In this study, it is possible that the data may not be positive simply due to the data collection process as accomplished by the patients. Dr. Ganley suggested Whitehall utilize a less subjective endpoint e.g. sleep duration. Whitehall should propose another endpoint for efficacy assessment. Whitehall stated they want to initiate this study in April and will develop a proposal as soon as possible. Dr. Katz requested that they submit a proposal including draft labeling to be used.

4. **Additional FDA comments and Whitehall response:**

- a) Chemistry request: Please include the source of the ibuprofen capsules used as controls. Please provide their specifications including appearance (shape, color, etc.).

Whitehall stated they would provide the information.

- b) The pharmacologist has not seen the animal study reports yet. The pharmacology and toxicology studies (mentioned in the Investigator's Brochure) appear to be adequate if there is no synergism in the toxicity.

Whitehall stated there were no synergistic toxicity findings.

**UNRESOLVED ISSUES:** Follow-up needed. See 3.c. above

**ACTION ITEMS:**

1. Whitehall will provide a proposal including draft labeling to be used as soon as possible (See 3.c.).
2. FDA Minutes of the meeting will convey to Whitehall within 30 days of the meeting date.

\_\_\_\_\_  
Leslie Vaccari  
Project Management Staff

Concur:

\_\_\_\_\_  
Karen Midthun, MD  
Division Director, DAAODP

cc: Orig IND 56,521  
HFD-550/Div File  
HFD-550/KMidthun/CFang/CChen/MZarifa/LVaccari/DBashaw/AAadebowale/LLu  
HFD-120/PAndreason  
HFD-560/CGanley/LKatz/RNeuner/MBenson/LHu/MChang/TParmalee/DLumkins/  
/KRothschild  
HFD-105/RDeLap

Drafted by:LAV/3-1-00/3-9-00

Initialed By: Christina Fang/no changes  
Conrad Chen/3-1-00  
Mona Zarifa/no changes  
Laura Lu/no changes  
Charles Ganley/3-2-00  
Linda Katz/3-3-00  
Linda Hu/3-3-00

Final:

Attachments: Whitehall's Overhead - 8 pages

**MEETING MINUTES**

E

4 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

## FDA MINUTES OF SPONSOR MEETING

**IND:** 56,521

**DATE:** 7/1/99

**PRODUCT NAME:** Ibuprofen/Diphenhydramine HCl Liqui-Gels, Advil PM

**SPONSOR:** Whitehall-Robins

**Whitehall-Robins Healthcare:**

Roger Berlin, M.D.	Executive Vice President, Scientific Affairs Worldwide
Stephen Cooper, DMD, Ph.D.	Vice President, Clinical Science and Medical Affairs
Mary Davis	Associate Director, Regulatory Affairs
Geraldine Doyle, Ph.D.	Director, Clinical Affairs
Ranga Geetha, Ph.D.	Director, Biostatistics
Sharon Heddish	Vice President, Regulatory Affairs Worldwide
Joel Waksman, Ph.D.	Senior Director of Biostatistics

**FDA:**

Robert DeLap, M.D., Ph.D.	Director, ODE V
Karen Mithun, M.D.	Acting Director, HFD-550
John E. Hyde, Ph.D., M.D.	Deputy Director
Charles Ganley, M.D.	Director, OTC Drug Products
Linda Katz, M.D.	Deputy Director, OTC Drug Products
Christina Fang, M.D.	Medical Officer
Linda Hu, M.D.	Medical Officer
Maria Lourdes Villalba, M.D.	Medical Officer
Sandra N. Cook	Project Manager
Stan Lin, Ph.D.	Team Leader, Statistics
Laura Lu, Ph.D.	Statistician
Michael Benson, R.Ph.	Regulatory Review Pharmacologist
Marina Chang, R.Ph.	Regulatory Review Pharmacologist
Debbie Lumpkins	Team Leader
Kerry Rothschild	Project Manager

**SUBJECT:** Whitehall-Robins (W-R) requested a teleconference to discuss their proposed clinical Multiple Use Safety and Compliance (MUSC) Study.

**Question 1**

**Is the MUSC study adequately designed for establishing the safety of Advil PM?**

The proposed study is not adequately designed to capture the safety information required by FDA. The proposed study should include the following:

- 3-arm safety study (1 liquigel vs. 2 liquigels vs. placebo)

- 300 patients per treatment arm
- recommend collecting efficacy on the 1<sup>st</sup> night of treatment
- the duration should be for 10 consecutive days
- the patient enrollment should emphasize the elderly population

**Question 2**

**Are the specified demographics of the intended study population appropriate?**

FDA recommends shifting the patient population toward the elderly (70% over 45 years, 25 – 30% over 65).

**Question 3**

**Are the specified statistical analyses for compliance, dosing patterns, efficacy, and safety appropriate?**

FDA would like Whitehall-Robbins to capture total adverse events. In addition, please measure general efficacy (global assessment) on the first night and at the end of the study.

**Question 4**

**If the dose-response study shows only marginal effect for a one capsule dose, can we reach agreement that the proposed MUSC study will provide sufficient exposure to support a two liquigel dose for the marketed product?**

See Question 1 for FDA's recommendations for study design.

**Question 5**

**Is the proposed *Uses* statement " For relief of occasional sleeplessness associated with — minor aches and pains" appropriate for Advil PM?**

The proposed statement appears reasonable to FDA.

  
Sandra N. Cook 8/21/97  
Project Manager

**MEETING MINUTES**



Whitehall-Robins  
Five Giralda Farms  
Madison, NJ 07940-0871  
Telephone (973) 660-5500  
Website address: <http://healthfront.com>

April 27, 1999

**IND 56,521**  
**Ibuprofen/Diphenhydramine - OTC**  
**Serial # 012**

**MINUTES: MARCH 26, 1999 TELECONFERENCE**

John Hyde, MD, Acting Director  
Division of Anti-inflammatory, Analgesic and  
Ophthalmic Drug Products (HFD 550)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Attention: Document Control Room N115  
9201 Corporate Boulevard  
Rockville, MD 20850

Dear Dr. Hyde:

Please refer to Whitehall-Robins Healthcare IND 56,521 submitted for a non-prescription analgesic/sleep-aid combination product containing ibuprofen and diphenhydramine, our meeting with the Agency on August 4, 1998 to discuss the clinical development program for this product, and our teleconference of March 26, 1999. Whitehall requested the March 26, 1999 teleconference to discuss an FDA request for a nighttime pharmacokinetics study, and also to obtain comment on our template for reporting pharmacokinetic studies to the Agency.

We appreciate the Agency's participation and have provided Whitehall-Robins' minutes for the March 26, 1999 teleconference (*attached*) for your review and comment. The format of the minutes is to provide Whitehall-Robins' question, followed by FDA's comment. We also request a copy of the Agency's minutes for the meeting when they become available.

If you have any questions concerning the teleconference or our draft minutes, please contact the undersigned at (973) 660-6031 or Mary Davis at (973) 660-5825.

Sincerely,

Hulon McCain, PhD  
Director  
Regulatory Affairs/Toxicology

Attachment

cc: Sandra N. Cook, Consumer Safety Officer  
Sharon A. Schmidt, Consumer Safety Officer

CONFIDENTIAL

19 - 449 - 34

**End Phase II/Pre-Phase III**  
**Teleconference of March 26, 1999**  
**(Agency did not provide their minutes)**

## FDA/WHITEHALL-ROBINS MEETING MINUTES

**Application:** IND 56,521

**Date:** March 26, 1999

**Product:** Advil PM LiquiGels (ibuprofen/diphenhydramine HCl, OTC)

### FDA

E. Dennis Bashaw, PharmD  
Pharmacokinetics Team Leader

Sandra Cook  
Project Manager

### Whitehall-Robins Healthcare

Stephen Cooper, DMD, PhD  
Vice President, Clinical and Medical Affairs

Sharon Heddish  
Vice President, Regulatory Affairs Worldwide

Geraldine Doyle, PhD  
Director, Clinical Research

Joel Waksman, PhD  
Senior Director of Biostatistics

Ranga Geetha, PhD  
Director of Biostatistics

Hulon McCain, PhD  
Director, Regulatory Affairs/Toxicology

Mary Davis  
Associate Director, Regulatory Affairs

Shyamalie Jayawardena, PhD  
Senior Statistician

Whitehall-Robins Healthcare (WRH) asked for this teleconference to discuss FDA's request for a nighttime pharmacokinetics study to support approval of this project. We also wished to obtain FDA's comments on WRH's draft template for reporting pharmacokinetic studies to the Agency. WRH questions are presented in bold followed by FDA comment.

- 1. WHR does not believe that a nighttime pharmacokinetic study should be required to support the safety and efficacy of Advil PM. WHR believes that such a study would provide no additional data than is being generated to demonstrate efficacy of Advil PM following nighttime administration in the ongoing clinical efficacy studies.**

FDA has concluded that as the product is not a controlled release formulation, a nighttime PK study will not be required to support safety and efficacy of this product.

The following questions referred to the presentation of results of bio-equivalence studies:

- 2. For blood samples taken either earlier or later than the times specified in the protocol, the times will be adjusted in the data set to reflect the actual times at which the samples were obtained. These deviations will be flagged with "T" in the concentration data tables. In the computation of pharmacokinetic parameters, the actual time of the blood draw will be used. However, in the computation of the mean concentration at each scheduled time point, concentrations with time deviations will be used as if the sample was collected at the scheduled time point. Is this procedure acceptable? If not, should time windows be established for blood draws? If so, how should data outside the windows be adjusted?**

The Agency stated that significant deviations from scheduled time points should be acknowledged. The width of the time window will depend upon the specific time point in question:  $\pm$  xx minutes, xx to be set to 20% if scheduled time point is within the first 12 hours after dosing, and as deemed reasonable when time points are farther apart.

3. **Currently the protocols require both pre- and post-study safety laboratory evaluations. Is a post-study laboratory evaluation (CBC and chemistry) necessary?**

Pre-study laboratory evaluation is needed for subject screening and determination of eligibility. However, for PK studies evaluating drugs which have been well studied, there is no reason to repeat the lab at the end of the study.

4. **Is FDA comfortable with the software (Win Nonlin<sup>®</sup>) we propose to use to calculate the PK parameters?**

FDA indicated that they have accepted data submitted by other companies using Win Nonlin<sup>®</sup> Software (for the calculation of the PK parameters) and would presumably continue to do so.

5. **Gender issues: Vd and Cl will be computed routinely but analyzed statistically only if either a gender or gender-by-treatment interaction exists. Is this acceptable?**

Descriptive statistics for Vd and Cl should be provided at the very least, but formal statistical analyses using GLM type models would be required if gender and treatment-by-gender interactions are significant. Although formal analyses are not routinely required if only the gender effect is significant, doing these analyses (and presenting the data) would be acceptable in any case.

6. **Is it necessary to include SAS<sup>®</sup> GLM output for all PK parameters, or is it sufficient to present only output for AUCI, AUCL, and Cmax (untransformed and log transformed)?**

It is sufficient to provide SAS outputs from analyses of the key parameters AUCI, AUCL, and Cmax (only for the transformed values).

7. **Should analyses and confidence intervals be presented for all parameters? If so, on what should the confidence interval for Tmax be based?**

Confidence intervals for the key parameters AUCI, AUCL, and Cmax will need to be presented. Analyses for Tmax should be limited to descriptive statistics.

8. **Should the spaghetti plots include subjects who do not complete all phases of the study (and therefore are not included in the statistical analyses of PK parameters)?**

"Spaghetti Plots" do not need to include subjects who dropped from the study for non-treatment related reasons but should include subjects who were dropped for any suspected treatment-related events.

**Post Meeting Note:** Drs. Bashaw and Waksman held a follow-up discussion on 4/23/99 to obtain clarification of several issues arising from the 3/26/99 teleconference. The following is a summary of the discussions.

- Time window deviations: Time points outside the reasonably chosen window should be listed under the scheduled time point and flagged in the individual listings but should *not* be included in time point summary statistics. Time points that deviate from the scheduled time points but are within the windows need not be flagged and should be included in the respective time point calculations. Calculation of pK parameters should be based on the *actual* time of the assessment regardless of whether the assessments were inside or outside the respective time windows.
- A proposal to leave out carryover effects from the primary analysis of bioavailability studies was acceptable as long as carryover effects were tested. In the event of significance, Whitehall-Robins would re-test for bioequivalence with carryover in the model, to assess its robustness, although the primary test would still be based on the model without carryover.
- The soon-to-be-submitted Advil PM bioavailability study did not completely follow our template and thus, should not be used by Dr. Dennis Bashaw to complete his review of the template. When Whitehall-Robins does complete a biostudy which completely follows our template model, we will provide this for his review and indicate that the report should be reviewed against the template provided to him.

**APPEARS THIS WAY  
ON ORIGINAL**

ORIGINAL  
N-006-GC

Whitehall-Robins  
Five Giralda Farms  
Madison, NJ 07940-0871  
Telephone (973) 660-5500  
Website address: <http://healthfront.com>



January 13, 1999

INDs 44,767/56,521  
Ibuprofen/Diphenhydramine-OTC  
Serial No. 028/No:006

**General Correspondence: Follow-up of August 4, 1998 Meeting**

John Hyde, MD, Acting Director  
Division of Anti-inflammatory, Analgesic, and  
Ophthalmic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, MD 20850

Dear Dr. Hyde:

Please refer to Whitehall-Robins Healthcare INDs 44,767 and 56,521 submitted for nonprescription analgesic/sleep-aid combination products containing ibuprofen and diphenhydramine. Specific reference is made to the Agency's minutes outlining agreements reached regarding the clinical program on August 4, 1998.

Submitted herewith is an updated summary of the clinical development program for Advil PM Liqui-Gels (see Attachment 1). This summary outlines our completed and current clinical activities underway in support of this combination product. This program reflects the following agreements reached at our August 4, 1998 meeting:

- A partial factorial design study is recommended to show at minimum that the combination product performs significantly better than ibuprofen alone for the sleep-aid indication in patients with pain (see studies AE 98-01 and AE98-02).
- The Agency would consider data from one strong dental pain trial plus the data from the pilot study as acceptable support for the combination; however, FDA would prefer data from two trials (see studies AE 98-01 and AE 98-02).
- The primary endpoints in all efficacy studies are the cumulative proportion of subjects asleep at 60 minutes post-dose for measuring sleep efficacy and SPRID at 120 minutes for pain efficacy. Sleep latency, duration of sleep, and sleep quality are evaluated as secondary parameters.
- A safety study will be conducted to increase the database (see study AE 97-08).



✓ MD  
JH/1/99  
Villalobos

- A dose response study to evaluate the efficacy of two Advil PM Liquigels (IBU 400mg/DPH HCl 50mg) compared to one Advil PM Liquigel (IBU 200mg/DPH HCl 25mg) will be conducted (see study AE 98-03).
- A study will be conducted in tension headache (see study AE 98-04).
- Data needs to be presented demonstrating that the release and absorption of the individual components in the finished dosage form are unchanged when given at bedtime. Whitehall is reviewing the literature and will be in contact with the Agency upon completion of our review of the data.
- WHR has successfully completed a pharmacokinetic/bioavailability study and a bioequivalence food effects study (see studies WM 716 & AE 97-02). The Agency has indicated these studies are acceptable. A relative bioavailability study is ongoing (see study AE 97-09) using the PM Liqui-Gel versus marketed single entity components.

We believe this program accurately reflects the agreements reached at our meeting on August 4 and outlined in our correspondence of August 14, 1998 and your fax of September 10, 1998 (attached). We request your concurrence that the studies, if successful, will fulfill the requirements for NDA approval.

Please contact the undersigned at (973) 660-5753 or Dr. Hulon McCain at (973) 660-6031 if you have any comments or questions.

Sincerely,



Sharon Heddish  
Vice President  
Regulatory Affairs Worldwide

**ATTACHMENT I**  
**Advil PM Liqui-Gels**  
**Revised Clinical Development Program**

<b>Protocol No.</b>	<b>Model</b>	<b>Design</b>	<b>Tx Groups</b>	<b>Sample Sizes</b>	<b>Objective(s)</b>	<b>Primary Endpoints</b>
WM-716*	PK/Bioavailability Study	Single-dose, single-center, inpatient, randomized, open-label, three-way crossover	2 diphenhydramine citrate capsules 2 ibuprofen capsules + 2 diphenhydramine citrate capsules	n=23	To compare the PK/bioavailability of ibuprofen 200mg capsules and diphenhydramine citrate 38mg capsules administered simultaneously to that of each drug individually.	Log transformed AUCL, AUCI and Cmax
AE-97-02*	Bioequivalence/Food Effect	Single-dose, single-center, inpatient, randomized, stratified (by gender), open-label, three-way crossover	2 Advil PM liquigels (fasted) 2 Advil PM liquigels (fed) 2 ibuprofen liquigels + 2 diphenhydramine HCl liquigels (fasted)	n=25	To compare the rate and extent of absorption of from: a) Advil PM liquigels (IBU 200mg/DPH HCl 25mg) under fasted and fed conditions b) Advil PM liquigels (IBU 200mg/DPH HCl 25mg) under fasted conditions compared to IBU 200mg liquigels and DPH HCl 25mg liquigels individually under fasted conditions	Log transformed AUCL, AUCI and Cmax
AE-97-09	Relative Bioavailability	Single-dose, single-center, inpatient, randomized, stratified (by gender), open-label, four-way crossover	2 Advil PM liquigels (fasted) 2 Advil liquigels (fasted) 2 Benadryl softgels (fasted) 2 Nuprin tablets (fasted)	n=24	To compare the rate and extent of ibuprofen absorption from Advil PM liquigels to Advil liquigels and Nuprin tablets. To compare the rate & extent of diphenhydramine absorption from Advil PM liquigels to Benadryl softgels.	Log transformed AUCL, AUCI and Cmax

Protocol No.	Model	Design	Tx Groups	Sample Sizes	Objective(s)	Primary Endpoints
AE-98-01	Oral Surgery	Single-dose, single-center, inpatient, randomized, stratified (by baseline pain and gender), double-blind, parallel, modified factorial	2 Advil PM liquigels 2 ibuprofen liquigels PBO	n=120 n=120 n=40	To evaluate the analgesic and sedative efficacy of Advil PM (IBU 400mg/DPH 50mg) compared to ibuprofen liquigel (ibuprofen 400mg) and placebo in subjects who are experiencing oral surgery pain and accompanying sleeplessness.	<u>Sleep</u> Cum. % asleep at 60 min. <u>Pain</u> SPRID 0-120 min.
AE-98-02	Oral Surgery	Single-dose, single-center, inpatient, randomized, stratified (by baseline pain and gender), double-blind, parallel, modified factorial	2 Advil PM liquigels 2 ibuprofen liquigels PBO	n=120 n=120 n=40	To evaluate the analgesic and sedative efficacy of Advil PM (IBU 400mg/DPH HCl 50mg) compared to ibuprofen liquigel (ibuprofen 400mg) and placebo in subjects who are experiencing oral surgery pain and accompanying sleeplessness.	<u>Sleep</u> Cum. % asleep at 60 min. <u>Pain</u> SPRID 0-120 min.
AE-98-03	Oral Surgery	Single-dose, single-center, inpatient, randomized, stratified (by baseline pain and gender), double-blind, parallel, dose-response	2 Advil PM liquigels 1 Advil PM liquigel PBO	n=120 n=120 n=40	To evaluate the analgesic and sedative efficacy of IBU 400mg/DPH HCl 50mg and IBU 200mg/DPH HCl 25mg compared to each other and placebo in subjects who are experiencing pain following oral surgery and are also having difficulty in falling asleep.	<u>Sleep</u> Cum. % asleep at 60 min. <u>Pain</u> SPRID 0-120 min.

Protocol No.	Model	Design	Tx Groups	Sample Sizes	Objective(s)	Primary Endpoints
AE-98-04	Headache	Single-dose, single-center, inpatient, randomized, stratified (by baseline pain and gender), double-blind, parallel	2 Advil PM liquigels PBO	n=80 n=80	To evaluate the analgesic and sedative effects of a single dose of IBU 400mg/DPH HCl 50mg compared to placebo in subjects experiencing either chronic or episodic tension headache and accompanying sleeplessness.	<u>Sleep</u> Cum. % asleep at 60 min. <u>Pain</u> SPRID 0-90 min.
AE-97-08	Multiple-Use Safety and Compliance Study	Multiple-dose, 5-center, outpatient, randomized, double-blind, parallel	1-2 Advil PM liquigels PBO	n=300 n=150	To evaluate Advil PM in a large sample population for: safety in use, compliance with directions and indications for use, drug consumption patterns, and efficacy.	<u>Compliance</u> - Compliance with dosing instructions and indications for use <u>Safety</u> - All AEs that occur within 24 hours of taking study medication <u>Efficacy</u> - Average assessment of pain relief and sleep over treatment days

\* Indicates study has been completed



Whitehall-Robins  
Five Giralda Farms  
Madison, NJ 07940-0871  
Telephone (973) 660-5500  
Website address: <http://healthfront.com>

August 14, 1998

IND 44,767  
Ibuprofen/Diphenhydramine -OTC  
Serial # 027

**General Correspondence: Comments on Meeting Minutes**

John Hyde, MD, Acting Director  
Division of Anti-inflammatory, Analgesic and  
Ophthalmic Drug Products (HFD 550)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, MD 20850

Dear Dr. Hyde:

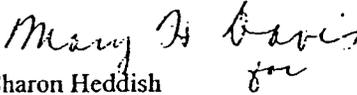
Please refer to Whitehall-Robins Healthcare IND 44,767 submitted for a non-prescription analgesic/sleep-aid combination product containing ibuprofen and diphenhydramine hydrochloride. Specific reference is made to a facsimile transmission of August 4, 1998 from Ms. Sandra Cook. This facsimile provided the Agency's responses to Whitehall questions regarding requirements for the clinical development program, which were presented in our pre-meeting package and discussed at the August 4<sup>th</sup> meeting.

We have reviewed the Agency's responses and feel they reflect the Agency's initial views presented at the meeting but do not, in some instances, reflect the outcome of the discussions at the meeting. Accordingly, for the responses at issue IA-C, we have prepared comments delineating our understanding of the agreements reached on these specific issues.

We understand from Ms. Cook that minutes of the meeting have been prepared and are circulating within the Agency for comment. We respectfully request that the attached comments be included in the minutes. We hope the Agency will review these comments favorably and issue minutes which reflect these agreements.

Please contact the undersigned at (973) 660-5753 or Dr. Hulon McCain at (973) 660-6031 if you have any comments or questions.

Sincerely,

  
Sharon Heddish  
Vice President  
Regulatory Affairs Worldwide

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**Question 1-A:** Are the modified oral surgery and inpatient headache models, with phase advancement incorporated into the design, appropriate for evaluating the efficacy of analgesic/sleep-aid products?

**FDA Response to be clarified:** A transient insomnia model, with phase advancement, is not considered reliable.

**WHR Comment:** The Agency indicated that their Neuropharmacology Group had expressed reservations regarding the use of models with phase advancement. However, in view of the need to simultaneously measure both sleep and pain endpoints, we understood from the discussions at the meeting that the models, as presented, were acceptable and represented the best available for the evaluation of OTC conditions.

**Question 1-B:** Is the cumulative proportion of subjects asleep at 60 minutes post-dose an appropriate primary measure of sleep efficacy and SPRID up to 120 minutes an appropriated measure of pain efficacy in these trials?

**FDA Response to be clarified:** Sleep latency, duration of sleep, and sleep quality are the efficacy parameters for sleep evaluation.

**WHR Comment:** The Agency requested and Whitehall agreed to provide justification for the use of the two proposed primary endpoints - cumulative proportion of subjects asleep at 60 minutes post-dose for measuring sleep, and SPRID at 120 minutes for pain efficacy. It was agreed that sleep latency, duration of sleep and sleep quality would be evaluated as secondary parameters. It was our understanding from the meeting that the Agency was in agreement with this proposal.

**Question 1-C:** Will the successful completion of two oral surgery studies provide sufficient efficacy data for approval for general indications as an analgesic/sleep aid? —

**FDA Response to be Clarified:** Whitehall-Robins needs to substantiate the sleeplessness claim in two models.

**WHR Comment:** We left the meeting believing we had agreement that one very strong modified factorial study, if successful, would be sufficient to support the proposed label claims for this product. The clinical development program would then consist of the following studies:

- One very strong study in the oral surgery model demonstrating superior efficacy of the combination of IBU 400 mg/DPH 50 mg over IBU 400 mg, along with supporting data from the pilot studies would meet Agency requirements. The two primary efficacy endpoints for this study will be cumulative proportion of subjects asleep at 60 minutes post dose, and SPRID 0-120 minutes for pain, with Whitehall providing a rationale for these primary endpoints.
- One dose-response study in the oral surgery model comparing efficacy of one Advil LiquiGel (IBU 200 mg/DPH 25 mg), two Advil LiquiGels (IBU 400 mg/DPH 50 mg) and Placebo. The two primary efficacy endpoints for this study will be cumulative proportion of subjects asleep at 60 minutes post dose, and SPRID 0-120 minutes for pain, with Whitehall providing a rationale for the endpoints.

- One two arm study in the headache model with two Advil LiquiGels (IBU 400 mg/DPH 50 mg) and Placebo — The primary endpoints for this study will be cumulative proportion of subjects asleep at 60 minutes post dose, and SPRID 0-90 minutes for pain.

**Additional Comments:**

**Actual Use Trial:** An actual use clinical trial is not required; however, it may be a means to provide additional patient exposure. The Agency requested and Whitehall agreed that if an actual use trial were not done, there would be increased enrollment in the efficacy trials to provide additional exposure information.

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liquigels to a currently marketed ibuprofen tablet formulation, a currently marketed ibuprofen liquigel formulation and a currently marketed diphenhydramine liquigel formulation is a clinically relevant comparison?

Whitehall-Robins needs to present data that the release and absorption of the individual components in the finished dosage form are unchanged when given at bedtime. The data can consist of an *in vivo* study or may be available in published literature. The proposed bioavailability and food/fast studies are acceptable to FDA.

*Sandra N. Cook*  
Sandra N. Cook 9/10/98  
Project Manager