CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-587

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

EXCLUSIVITY SUMMARY for NDA # 21-587 SUPPL #

Trade Name: Children's Advil® Allergy Sinus

Generic Name: ibuprofen 100 mg/pseudoephedrine HCl 15 mg/chlorpheniramine maleate 1 mg/5 mL

Applicant Name: Wyeth Consumer Healthcare

HFD-550

Approval Date: February 24, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES /_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)?

   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 /_X__/ 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.

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

d) Did the applicant request exclusivity?

YES /___/ NO /_**X**__/

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

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

YES /___/ NO /_**X**__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_**X**__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_**X**__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the

combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X__/ NO /___/

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

NDA # **17-463 (ibuprofen)**

NDA # **17-603 (pseudoephedrine)**

NDA # **7-638 (chlorpheniramine)**

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (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 /_**X**__/ 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 9:**

   (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 /_**X**__/

   (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 /_X__/

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 /_X__/

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:

Investigation #1, Study # **AR-00-04**

Investigation #2, Study #

Investigation #3, Study #

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 **AR-00-04** YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

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

Investigation #1 YES /___/ NO /_**X**__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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"):

Investigation #_**1**_, Study # **AR-00-04**

Investigation #__, Study #

Investigation #__, Study #

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 # **63,999** YES /**X**/	NO /___/ Explain:
Investigation #2	
IND # _____ 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? **N/A**

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: _____

_____

_____

Jane A. Dean, RN, MSN
Signature of Preparer
Project Manager
Title

February 24, 2004
Date

Charles Ganley, MD, DOTCDP, HFD-560
Signature of Office or Division Director

February 24, 2004
Date

cc:
Archival NDA 21-587
HFD-550/Division File
HFD-560/Division File
HFD-550/Jane A. Dean
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347

Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Charles Ganley
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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA **21-587**	Efficacy Supplement Type SE-	Supplement Number	
Drug: **ibuprofen 100 mg/pseudoephedrine HCl 15 mg/ chlorpheniramine maleate 1 mg/5 mL suspension**		Applicant: **Wyeth Consumer Healthcare**	
RPM: **Jane A. Dean, RN, MSN**		HFD-**550**	Phone # **301-827-2536**
Application Type: **(X)** 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): **n/a**	

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	**NSAID Combination Product**
• Other (e.g., orphan, OTC)	**OTC**
❖ User Fee Goal Dates	**February 24, 2004**
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
User Fee Information	
• User Fee	**(X)** Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No
• This application is on the AIP	( ) Yes **(X)** No
• Exception for review (Center Director's memo)	**n/a**
• OC clearance for approval	**n/a**
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(X)** Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	**(X)** Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (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).	( ) Verified

Exclusivity (approvals only)	
• Exclusivity summary	**February 24, 2004**
• 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)*	**July 25, 2004**
General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**n/a**
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** 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)	**X**
• Most recent applicant-proposed labeling	**X**
• Original applicant-proposed labeling	**X**
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**January 6, 2004 (DMETS)** **November 12, 2003 (DMETS)** **November 5, 2003 (DOTCDP)** **February 23, 2004 (DOTCDP)**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**n/a**
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	**n/a**
• Applicant proposed	**X**
• Reviews	**November 5, 2004 (DOTCDP)** **February 23, 2004 (DOTCDP)**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**X**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**X**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**X**
❖ Memoranda and Telecons	**n/a**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**n/a**
• Pre-NDA meeting (indicate date)	**January 8, 2003**
• Pre-Approval Safety Conference (indicate date; approvals only)	**n/a**
• Other	**n/a**

Advisory Committee Meeting	
• Date of Meeting	n/a
• 48-hour alert	n/a
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	n/a
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	February 11, 2004 (HFD-560 Medical Team Leader) February 24, 2004 (HFD-560 Division Director)
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	November 14, 2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	n/a
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	November 14, 2003 (Clinical Review)
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	n/a
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	n/a
❖ Demographic Worksheet *(NME approvals only)*	n/a
❖ Statistical review(s) *(indicate date for each review)*	n/a
❖ Biopharmaceutical review(s) *(indicate date for each review)*	December 24, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	n/a
Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	X
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	February 13, 2004 (two reviews)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	February 13, 2004 (review #1)
• Review & FONSI *(indicate date of review)*	n/a
• Review & Environmental Impact Statement *(indicate date of each review)*	n/a
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	n/a
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	November 17, 2003
Nonclinical inspection review summary	n/a
Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	n/a
❖ CAC/ECAC report	n/a

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/s/

Jane Dean

2/24/04 04:37:16 PM

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Division of OTC Drug Products Labeling Review

NDA 21-587

Submission Dates: February 6 and 13, 2004
Review Date: February 20, 2004

Applicant:
Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Applicant's Representative:
Lauren Quinn
Associate Director, Regulatory Affairs
973-660-6806

Drug:
Children's Advil® Allergy Sinus, and [redacted] (ibuprofen 100 mg/ 5 mL, pseudoephedrine hydrochloride 15 mg/ 5 mL, chlorpheniramine maleate 1 mg/5 mL Suspension)

Pharmacologic Category:
pain reliever/fever reducer/nasal decongestant/ antihistamine

Submitted:
(1) revised 1 fl oz., [redacted] and 8 fl oz. carton and container labels for berry flavor Children's Advil® Allergy Sinus Suspension
(2) [redacted]

Background:
Sponsor submitted draft labeling August 23, 2003 and October 22, 2003. The Agency recommended revisions by faxes of November 6, 2003, January 15, 2004, and a telephone conversation of January 20, 2004.

Reviewer's Comment:
(1) Revisions were made and labels are acceptable.
(2) The sponsor is withdrawing the [redacted] labeling in the 2/6/04 submission and this is acceptable.

Recommendation:
(1) An approval letter can be issued to the sponsor for the 1 fl oz. [redacted] and 8 fl oz. sizes of Children's Advil® Allergy Sinus Suspension, berry flavor.

(2) Note to the sponsor that the Agency is accepting the sponsor's request to withdraw the [redacted]" labeling without prejudice, and the sponsor has the right to submit this additional labeling in the future as a prior approval supplement.

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

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

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/s/

Michael Benson
2/23/04 08:37:13 AM
INTERDISCIPLINARY

Marina Chang
2/23/04 09:03:12 AM
INTERDISCIPLINARY

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Division Director Memo

NDA #: 21-587

Drug Name: ibuprofen 100 mg/5 ml, Pseudoephedrine HCL 15 mg/5 ml, chlorpheniramine maleate 1 mg/5ml

Proprietary Names: Children's Advil® Allergy & Sinus

Sponsor: Wyeth Consumer healthcare

Receipt Date: April 23, 2003

PDUFA Date: February 24, 2004

Type of Document: NDA supplement

Date: February 23, 2004

Conclusions/Recommendation

1. I concur with Dr. Andrea Leonard-Segal's review.
2. Labeling and CMC reviews were pending at the time of Dr. Segal's review. They have subsequently been completed and the reviewers have given an approval recommendation. I concur with their reviews and recommendations.
3. I agree with the approval recommendation from Dr. Segal and the Phase 4 commitment.
4. The phase 4 commitment submitted by the sponsor is adequate.

Charles J. Ganley, M.D.

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/s/

Charles Ganley
2/24/04 12:49:19 PM
MEDICAL OFFICER

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
9201 Corporate Boulvard
Rockville, MD 20850

To: David Smith, PhD	**From:** Ms. Jane A. Dean, RN, MSN
Fax: 973-660-8698	**Fax:** 301-827-2531
Phone: 973-660-6806	**Phone:** 301-827-2090
Pages: 1 (including cover page)	**Date:** 2-23-2004
Re: NDA 21-587 – Telecon with FDA on 2-23-04 clarifying the Post Marketing Commitment	

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

Comments: Dear David, this fax is to provide the necessary documentation you will need in providing clarification of Wyeth's proposed Post Marketing Commitment in your 2-19-04 letter. As discussed today with Dr. Andrea Leonard-Segal, Medical Team Leader from DOTCDP, please use the language specified in the comments from the Agency fax of 2-9-04 when describing the post marketing commitment. Also, you may add the word "Advil" between "children's" and "products" so as to clearly identify which products you will be using in the protocol. The language should read as follows:

- A study to answer the question of the consumers ability to identify different ingredients in different children's Advil products (including triple combination products, double combination products and single active ingredient products) and ability to select the correct product for their symptoms.

Sincerely,

Jane Dean
Project Manager

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/s/

Jane Dean
2/23/04 06:24:31 PM

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Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
9201 Corporate Boulvard
Rockville, MD 20850

To:	David Smith, PhD	**From:**	Ms. Jane A. Dean, RN, MSN
Fax:	973-660-8698	**Fax:**	301-827-2531
Phone:	973-660-6806	**Phone:**	301-827-2090
Pages:	2 (including cover page)	**Date:**	February 9, 2004
Re:	NDA 21-587 – Post Marketing Commitments comments		

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

Comments: Dear David, the following is an example of the wording that goes into an action letter with regards to Post Marketing Commitments:

"We remind you of your postmarketing study commitment(s) in your submission dated DATE. These commitments are listed below.

LIST POSTMARKETING COMMITMENTS IN THE FOLLOWING FORMAT:

1. Description of Commitment (1 COMMITMENT= 1 STUDY):

DESCRIPTION
Protocol Submission: by MM/YY
Study Start: by MM/YY
Final Report Submission: by MM/YY

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected

summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence.**"

I hope you find this helpful. By submitting it in the above format, it truly saves time for both you and the Agency.

Based on Friday's telecon with Lauren Quinn, Sharon Heddish and yourself, I have summarized the goal for your post marketing commitment as follows:

- A study to answer the question of the consumers ability to identify different ingredients in different children's products (including triple combination products, double combination products and single active ingredient products) and ability to select the correct product for their symptoms.

As we said during the telecon, the type of study is up to your discretion as long as the goal is achieved. At this point in the process, the only thing we need from you is a letter indicating that you agree to this commitment. Note in the standard language that we don't need to have the actual protocol yet. The submission date will be determined by you.

If you have any questions, please feel free to call me at 301-827-2536.

Sincerely,

Jane Dean
Project Manager

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/s/

Jane Dean
2/9/04 06:17:37 PM

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: January 15, 2004

To: David S. Smith, Ph.D.	**From:** Elaine Abraham
Company: Wyeth Consumer Healthcare	Division of Over-the-Counter Drug Products
Fax number: (973) 660-8698	**Fax number:** (301) 827-2315
Phone number: (973) 660-6806	**Phone number:** (301) 827-2276

Subject: N 21-587 trade name

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

Message: Please refer to your new drug application NDA 21-587 dated April 23, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Children's Advil Allergy Sinus/ [redacted]. Your October 22, 2003, submission proposed changing the Advil trade name to ' [redacted]

The Division of Medication Errors and Technical Support (DMETS) does not recommend the use of " [redacted] is unacceptable because the proposed name does not adequately describe that the product contains a decongestant ingredient. This could be confusing to consumers because the adult product, which contains the same ingredients as the children's product, is called "Advil Allergy Sinus".

At this time, we are unlikely to find the name, [redacted]" acceptable without data supporting consumer comprehension of the product ingredients relative to other Advil cough cold products. You may wish to request a meeting with the Division in the future to discuss this issue.

The original Advil trade name submitted, "Children's Advil Allergy Sinus," is acceptable. Resubmit labeling with the "Children's Advil Allergy Sinus" trade name. We may also require a phase 4 commitment to evaluate whether consumers can distinguish between your various ibuprofen-containing combination products and select the correct product for their symptoms. Given our heightened concerns about the safe use of OTC drug products containing NSAIDs and sympathomimetics, we believe it is important to have label comprehension information on the ability of consumers to distinguish between combination and single ingredient products. If you would like to discuss this issue with us, please contact the project manager to arrange a teleconference.

In order to ensure a timely action for this new drug application, we request that you revise and resubmit the carton and container labels as soon as possible. To speed the review, you can E-mail your response to Elaine Abraham at Abraham@cder.fda.gov in addition to the submission to the document room.

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/s/

Elaine Abraham
1/15/04 02:36:26 PM
CSO

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Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
9201 Corporate Boulvard
Rockville, MD 20850

To: David Smith, PhD	**From:** Ms. Jane A. Dean, RN, MSN
Fax: 973-660-8698	**Fax:** 301-827-2531
Phone:973-660-6806	**Phone:** 301-827-2090
Pages: 1 (including cover page)	**Date:** 12-29-2003
Re: NDA 21-587 – Comments on Biopharm issues	

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

• **Comments:** Dear David, the following comment pertains to Biopharm issues:

- It is recommended that dissolution specification be tightened to Q = [redacted] in 10 minutes.

If you have any questions, please feel free to call me at 301-827-2536.

Sincerely,

Jane Dean
Project Manager

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/s/

Jane Dean
12/29/03 02:40:49 PM

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ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 16 2003

Paul Chervinsky, M.D.
Northeast Medical Research Associates, Inc.
49 State Road, Watuppa Building
North Dartmouth, Massachusetts 02747

Dear Dr. Chervinsky:

Between September 4 and 10, 2003, Paraluman S. Leonin, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # AR-00-04 entitled: "Children's Advil Allergy — Sinus Suspension Multiple Dose Safety Study in Children 6-<12 years of age with Symptoms Consistent with Allergic Rhinitis") of the investigational drug Children's Advil Allergy — Sinus Suspension, performed for Wyeth. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Investigator Leonin discussed with you via telephone the inspectional observations. We wish to emphasize that you did not conduct the study according to the investigational plan [21 CFR 312.60] in that subject 10095 did not meet inclusion criteria for height and met the exclusion criteria for blood pressure. A repeat blood pressure measurement was not performed.

Please make appropriate corrections to your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Leonin during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

/S/

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

CFN: 1280356
Field Classification: NAI
Headquarters Classification: VAI (no response required)

Deficiencies noted:
__X__ failure to adhere to protocol (05)
Deficiency codes: 05

cc:
HFA-224
HFD-550 Doc.Rm. NDA# 21-587
HFD-550 Review Div.Dir. Chambers
HFD-550 MO Fang
HFD-550 PM Dean
HFD-46/47c/r/s/ GCP File #306
HFD-47 Tesch
HFR-NE250 DIB Kravchuk
HFR-NE250 Bimo Madigan
HFR-NE250 Investigator Leonin
GCF-1 Seth Ray

r/d: (DT):10/22/03; 10/28/03; 11/18/03; 11/20/03
reviewed:JPS: 10/24/03; 10/29/03 (signed 1st ltr); 11/20/03
f/t:ml:10/28/03; 11/25/03

O:\Tesch\letters\chervinsky letter.VAI.doc

Reviewer Note to Rev. Div. M.O.

This was a high priority CDER User Fee NDA Pre-approval Clinical Investigator Data Validation Inspection of Dr. Paul Chervinsky. The site was chosen because of high enrollment. Records were found to be in good order. One subject failed to meet inclusion/exclusion criteria. The investigator discussed this with Dr. Chervinsky at the close of the inspection. No 483 was issued. The investigation was classified NAI by the field, and VAI by headquarters. Data are acceptable.

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/s/

Leslie Ball
12/16/03 04:34:36 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Grant C. Olson, M.D.
Colorado Asthma and Allergy Centers, P.C.
1667 Cole Boulevard, Building 19, Suite 205
Lakewood, Colorado 80401

DEC 16 2003

Dear Dr. Olson:

Between September 16 and 24, 2003, Ms. Linda Cherry, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol #AR-00-04 entitled: "Children's Advil Allergy Sinus Suspension Multiple Dose Safety Study in Children 6-<12 years of age with Symptoms Consistent with Allergic Rhinitis") of the investigational drug Children's Advil Allergy Sinus Suspension, performed for Wyeth Consumer Healthcare. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Cherry presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not conduct the study according to the investigational plan [21 CFR 312.60].

   a. Subjects 10051, 10056 and 10068 failed to meet inclusion/exclusion criteria. Subject 10051 was just below the 5th percentile for weight, an inclusion criterion. Subject 10056 was above the 95th percentile for height, an exclusion criterion. Subject 10068 was at the 90th percentile for blood pressure, an exclusion criterion.

   b. Subjects 10056, 10057, 10060, 10062, 10063, 10064, 10065, 10068, 10072, 10073, 10074 and 10075 did not have written comparisons made between their baseline and final visit vital signs.

   c. You failed to sign the PRN Medication Form for subjects 10056, 10060, 10065, 10066, 10067, 10070 and 10071.

   d. You failed to sign the Adverse Experiences Form for four occurrences of drowsiness for subject 1072.

   e. You failed to sign the Exclusion Criteria Form for subjects 10055, 10056, 10057, 10058, 10059, 10060, 10061, 10062, 10063 and 10071.

   f. You failed to review and sign the Final Visit End of Study Assessment form for subject 10060.

We trust that the corrective actions you have initiated, as described in you letter of October 1, 2003, will provide adequate measures to bring your site into compliance with FDA regulations. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Cherry during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

/S/

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3004121544
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__X__ 2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__X failure to adhere to protocol (05)
Deficiency Codes: 05

cc:
HFA-224
HFD-550 Doc.Rm. NDA#21-587
HFD-Chambers Review Div.Dir.
HFD-550 Fang MO
HFD-550 Dean PM
HFD-46/47c/r/s/ GCP File #11022
HFD-47 Tesch
HFR-SW240 Miller DIB
HFR-SW2520 Thompson Bimo Monitor
HFR-SW2520 Cherry Field Investigator
GCF-1 Seth Ray

r/d: Tesch: 10/29/03; 11/18/03; 11/19/03
reviewed: JPS:11/6/03; 11/19/03
f/t:ml: 11/25/03
O:\Tesch\letters\olson vai letter.doc

Reviewer Note to Rev. Div. M.O.

This was a routine PDUFA related investigation of Dr. Grant Olson. Dr. Olson was selected because of high enrollment. There was one serious protocol violation. A subject was enrolled with an unacceptably high blood pressure reading. All of the other violations were clerical and involved failure to sign off on various forms. Dr. Olson and his research supervisor both felt strongly that most of the problems would have been avoided if the study coordinator had been more vigilant.

Dr. Olson is aware that he is ultimately responsible for all aspects of the conduct of the trial. Dr. Olson addressed the observations made by the investigator and outlined corrective actions in a letter to the field office dated October 1, 2003.

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/s/

Leslie Ball
12/16/03 04:33:22 PM

Office of Drug Safety

Memo

To: Brian Harvey, MD, PhD
Acting Director, Division of Anti-Inflammatory Analgesic and Ophthalmologic Drug Products
HFD-550

From: Nora Roselle, PharmD
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Alina Mahmud, RPh
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

Jerry Phillips, RPh
Associate Director, Office of Drug Safety
HFD-400

CC: Jane Dean
Project Manager
HFD-550

Date: December 12, 2003

Re: ODS Consult 03-0203-1; Children's Advil Allergy (Ibuprofen, Pseudoephedrine, and Chlorpheniramine Suspension) 100 mg/15 mg/1 mg per 5 mL; NDA 21-587.

This memo is in response to a November 19, 2003 request from the Division of Anti-Inflammatory Analgesic and Ophthalmologic Drug Products (HFD-550), for the Division of Medication Errors and Technical Support (DMETS) to review the proprietary name Children's Advil Allergy.

DMETS reviewed the proprietary name Children's Advil Allergy Sinus on November 12, 2003, and found the name acceptable (see ODS consult 03-0203); however, on October 22, 2003, the sponsor submitted an amendment to the labeling which proposes to remove the word "Sinus" from the originally proposed name "Children's Advil Allergy Sinus". This is a combination product consisting of chlorpheniramine, ibuprofen, and pseudoephedrine. Each of the active ingredients has a certain role in the treatment of the patient: ibuprofen is a pain reliever/fever reducer, chlorpheniramine is an antihistamine, and pseudoephedrine is a nasal decongestant.

DMETS believes that removing the term "Sinus" from the proposed proprietary name may lead to confusion as the product "Advil Allergy Sinus" is also currently marketed by the sponsor. The proposed product, Children's Advil Allergy Sinus, contains the same active ingredients as Advil Allergy Sinus, except in half the amount. In the original proposed name "Children's Advil Allergy Sinus", "Advil" described the ibuprofen ingredient, "Allergy" described the chlorpheniramine ingredient, and "Sinus" described the pseudoephedrine ingredient. We believe that with the removal of the term "Sinus", a consumer may not recognize that pseudoephedrine is also contained in the children's product, as in the adult product, and may take additional pseudoephedrine, potentially leading to an overdose. Thus, DMETS believes there is potential for confusion and error with the proposed name change and does not recommend the use of the name, Children's Advil Allergy.

DMETS would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarification, please contact Sammie Beam, Project Manager, at 301-827-3242.

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/s/

Nora L. Roselle
1/6/04 10:15:20 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
1/6/04 10:42:02 AM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
1/6/04 11:25:20 AM
DRUG SAFETY OFFICE REVIEWER

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

REQUEST FOR CONSULTATION

TO (Division/Office):
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
PKLN Rm. 15B-23

FROM:
Jane A. Dean, RN, MSN, Project Manager HFD-550
x72536

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 19, 2003		21-587		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Children's Advil Allergy/ & Sinus Ibuprofen 100 mg/Pseudoephedrine 15 mg/Chlorpheniramine 1 mg per 5 ml (OTC)	Routine	3/S	December 19, 2003

NAME OF FIRM: Wyeth Consumer Healthcare

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: **Sponsor has recently submitted an amendment to labeling. Sponsor proposes removing the word "Sinus" from the originally proposed name "Children's Advil Allergy Sinus". DMETS has already done a review (ODS Consult # 03-0203) of the names Children's Advil Allergy Sinus/ [redacted] In light of the sponsor's proposed change in the name, does this change the conclusions reached in the DMETS review?**

PDUFA DATE: **February 22, 2004**
ATTACHMENTS: Copy of 10/22/03 letter with Draft Proposed Labeling and Carton Labels

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Jane A. Dean, RN, MSN, HFD-550 x72536	X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jane Dean
2/13/04 05:21:47 PM
ODS Consult # 03-0203-1 Review complete and memorandum sent 12-12-03 to HFD-550; memorandum in DFS

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 17, 2003 **DATE OF DOCUMENT:** July 11, 2003	**DESIRED COMPLETION DATE:** October 6, 2003	**ODS CONSULT #:** 03-0203

TO: Lee Simon, MD
Director, Division of Anti-Inflammatory Analgesic and Ophthalmologic Drug Products
HFD-550

THROUGH: Jane Dean
Project Manager
HFD-550

PRODUCT NAME: **Children's Advil Allergy Sinus** [redacted] (Ibuprofen, Pseudoephedrine, and Chlorpheniramine Suspension) 100 mg/15 mg/1 mg per 5 mL **NDA#:** 21-587	**NDA SPONSOR:** Wyeth Consumer Healthcare

SAFETY EVALUATOR: Nora Roselle, PharmD

SUMMARY: In response to a request from the Division of Anti-Inflammatory Analgesic and Ophthalmologic Drug Products (HFD-550), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names "Children's Advil Allergy Sinus" and [redacted] to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATION:

1. DMETS has no objections to the use of the proprietary name, "Children's Advil Allergy Sinus". However, DMETS does not recommend the use of the proprietary name, [redacted]
2. DMETS recommends implementation of the label and labeling recommendations outlined in section III of this review.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 25, 2003

NDA#: 21-587

NAME OF DRUG: **Children's Advil Allergy Sinus**

(Ibuprofen, Pseudoephedrine, and Chlorpheniramine Suspension)
100 mg/15 mg/1 mg per 5 mL

NDA HOLDER: Wyeth Consumer Healthcare

I. INTRODUCTION:

This consult is written in response to a request from the Division of Anti-Inflammatory Analgesic and Ophthalmologic Drug Products, for review of the proposed proprietary names Children's Advil Allergy Sinus The sponsor is seeking marketing approval for the children's formulation of the dual tradenames, Children's Advil Allergy Sinus for the same three identical active ingredients. The proposed labels and labeling were reviewed for possible interventions to minimize medication errors.

PRODUCT INFORMATION

Children's Advil Allergy Sinus are the proposed proprietary names for the combination product consisting of chlorpheniramine, ibuprofen, and pseudoephedrine. Both medications are proposed as over-the-counter (OTC) drug products. Children's Advil Allergy Sinus are indicated for the temporary relief of symptoms (runny nose, itchy/watery eyes, itching of the nose and throat, sneezing, nasal congestion, sinus pressure, headache, minor aches and pains, and fever) associated with hay fever or other upper respiratory allergies, and the common cold. The recommended dose of Children's Advil Allergy Sinus is 2 teaspoonfuls every six hours not to exceed 4 doses per day in children 48 to 95 pounds in weight or 6 to 11 years old. Each 5 mL contains 1 mg chlorpheniramine maleate, 100 mg ibuprofen, and 15 mg pseudoephedrine. The sponsor plans to market each medication in 1 ounce, 4 ounce, and 8 ounce bottles.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO.
[3] The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

that sound-alike or look-alike to Children's Advil Allergy Sinus and [redacted] to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis[4] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by DMETS to gather professional opinions on the safety of the proprietary names Children's Advil Allergy Sinus and [redacted] Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

- Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Children's Advil Allergy Sinus [redacted] These products are listed in Table 1 and Table 2 (see below and page 4) along with the dosage forms available and usual FDA-approved dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other
Children's Advil Allergy Sinus (OTC)	Oral Suspension: Chlorpheniramine maleate 1 mg/ Ibuprofen 100 mg/ Pseudoephedrine HCl 15 mg per each 5 mL teaspoon	Children 48-95 lbs or 6 - 11 years of age: 2 teaspoonfuls every 6 hours, not to exceed 4 doses per day	
Advil Allergy Sinus (OTC)	Tablet: Chlorpheniramine maleate 2 mg/ Ibuprofen 200 mg/ Pseudoephedrine HCl 30 mg	Adults: 1 caplet every 4 - 6 hours while symptoms persist	Look-alike, Sound-alike
Children's Advil (OTC)	Ibuprofen Chewable Tablet: 50 mg Oral Suspension: 100 mg/5 mL	Children's Chewable Tablet: Dose based on weight/age, given every 6 - 8hours not to exceed 4 doses per day Children's Oral Suspension: Dose based on weight/age, given every 6 - 8 hours not to exceed 4 doses per day	Look-alike, Sound-alike

*Frequently used, not all-inclusive.

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[4] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 2: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other
[redacted]	[redacted]	[redacted]	
Children's Dimetapp Cold & Allergy Elixir (OTC)	Oral Elixir: Brompheniramine maleate 1 mg/ Pseudoephedrine HCl 15 mg per each 5 mL teaspoon	Children 6 to under 12 years: 2 teaspoons every 4 hours Adults and Children 12 years and over: 4 teaspoons every 4 hours	Look-alike, Sound-alike

*Frequently used, not all-inclusive.

B. DMETS' Phonetic and Orthographic Analysis (POCA) database

DMETS' Phonetic and Orthographic Analysis (POCA) database was unavailable to search at the time of this review.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Six separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of Children's Advil Allergy Sinus and [redacted] with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 127 health care professionals (pharmacists, physicians, and nurses) for each name, respectively. These exercises were conducted in an attempt to simulate the prescription ordering process. Inpatient orders and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Children's Advil Allergy Sinus or [redacted] (see below and page 5). These prescriptions were optically scanned and were delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Children's Advil Allergy Sinus

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Children's Advil Allergy Sinus #1 tsp q6hrs prn #120mL	Children's Advil Allergy Sinus Two teaspoons every six hours as needed. One hundred twenty mL.
Inpatient RX: Children's Advil Allergy Sinus 2 tsp q6hrs prn 120mL	

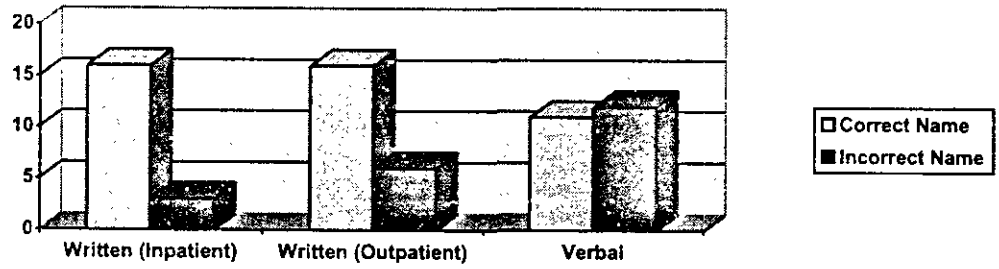
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Sig: 2 tsp q6hrs prn. 120 mL Inpatient RX: Children's Dimetapp Allergy Sinus 2 tsp q6h prn 120 mL	He is to get two teaspoons every six hours as needed. Dispense one hundred twenty mL.

2. Results:

The results for **Children's Advil Allergy Sinus** are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	19 (44%)	16 (84%)	3 (16%)
Written Outpatient	41	22 (54%)	16 (73%)	6 (27%)
Verbal	43	23 (53%)	11 (48%)	12 (52%)
Total	127	64 (50%)	43 (67%)	21 (33%)



Among the written inpatient prescription study participants for Children's Advil Allergy Sinus, 3 of 19 (16%) participants interpreted the name incorrectly. The incorrect responses were *Childrens Advil Allergy and Sinus (1), Childrens Tyenol Allergy Sinus (1),* and *Childrens Tylenol (1).* Childrens Tylenol is the name of a drug product currently marketed in the United States as both an oral suspension and chewable tablet.

Among the written outpatient prescription study participants for Children's Advil Allergy Sinus, 6 of 22 (27%) participants interpreted the name incorrectly. The incorrect responses were *Children's Advil Allergy & Sinus (3), Childrens Advil Allergy Adira (1), Childrens Allergy and Sinus (1),* and *Children Advil Allergy Sinus (1).* None of the incorrect responses are names of currently marketed drug products.

Among the verbal prescription study participants for Children's Advil Allergy Sinus, 12 of 23 (52%) of the participants interpreted the name incorrectly. The incorrect responses were *Children's Advil Allergy and Sinus (7), Children's Advil Allergy & Sinus (2), Childrens Advill Allergy and Sinus (1), Childres Advil Allergy Sinus (1),* and *Children's Advil (1).* Children's Advil is the name of a drug product currently marketed in the United States as both an oral suspension and chewable tablet.

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

E. SAFETY EVALUATOR RISK ASSESSMENT:

1. Children's Advil Allergy Sinus

Currently, there are five Children's Advil products in the U.S. market: Children's Advil Drops, Children's Advil Suspension, Children's Advil Chewables, Children's Advil Jr. Strength Coated Tablets, and Children's Advil Cold. In addition, the name Advil Allergy Sinus is already on the market. The proposed Children's Advil Allergy Sinus formulation is half the strength of the adult version, Advil Allergy Sinus. Historically, these names were not reviewed by DMETS.

In reviewing the proposed proprietary names "Children's Advil Allergy Sinus", the primary concerns raised were related to three look-alike and/or sound-alike names. The products considered to have potential for name confusion with Children's Advil Allergy Sinus were Advil Allergy Sinus, Children's Advil, and Children's Tylenol.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Children's Advil Allergy Sinus could be confused with Children's Advil. One respondent from the verbal study interpreted the name to be Children's Advil. In addition, one respondent from the written inpatient study incorrectly interpreted the name to be Childrens Tylenol, a drug product currently marketed in the United States as both an oral suspension and chewable tablet. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. In addition, one study participant commented that "I assume that 'Children's' indicates the strength."

a. Advil Allergy Sinus was identified to have a look and sound-alike similarity to Children's Advil Allergy Sinus. Advil Allergy Sinus is an over-the-counter (OTC) combination product consisting of chlorpheniramine maleate (2 mg), ibuprofen (200 mg), and pseudoephedrine HCl (30 mg). It is available as oral caplets dosed as one every 4 to 6 hours. The two names share the name "Advil Allergy Sinus" differing only by the word "Children's" in front of the proposed name. The extension of over-the-counter proprietary names is a common practice for many OTC products. A search of the AERS database did not reveal any medication error reports among the Advil product line, therefore DMETS believes that the potential for confusion between Advil Allergy Sinus and Children's Advil Allergy Sinus is minimal. However, we will continue to monitor the product in the post-marketing phase.

b. Children's Advil was identified to have sound-alike and look-alike potential with the proposed proprietary name, Children's Advil Allergy Sinus. Children's Advil is available as both a 50 mg ibuprofen chewable tablet and a 100 mg ibuprofen oral suspension. Children's Advil is used in the temporary relief of fever and minor aches and pains due to the common cold, flu, sore throat, headaches, and toothaches. The names Children's Advil and Children's Advil Allergy Sinus differ in that the proposed name

contains the modifier "Allergy Sinus". DMETS is concerned that the current presentation of the proposed name on labels and labeling may aid in the confusion between Children's Advil and Children's Advil Allergy Sinus since the modifier "Allergy Sinus" appears in a different color and print than the parent name Children's Advil. It is possible that the "Allergy Sinus" portion of the name can be left off on an order and could possibly be misinterpreted as one of the other existing Children's Advil products. This is evidenced by the verbal prescription study which showed that one respondent interpreted the name to be "Children's Advil", leaving off the descriptor "Allergy Sinus". However, Children's Advil Allergy Sinus is an Advil product line extension. The extension of over-the-counter proprietary names is a common practice for many OTC products. A search in the AERS database did not reveal any medication error reports among the Advil product line. Therefore, DMETS has minimal concerns with the use of Children's Advil Allergy Sinus.

c. Children's Tylenol was identified to have look-alike similarity with Children's Advil Allergy Sinus. From the inpatient study, one respondent incorrectly interpreted the name as Childrens Tylenol. Children's Tylenol (acetaminophen) is available in oral suspension and chewable tablet dosage forms. The oral suspension dosage form consists of 160 mg of acetaminophen per 5 mL and the chewable tablet contains 80 mg acetaminophen per tablet. Doses of each are based on either weight or age and can be repeated every four hours, not to exceed five doses in 24 hours. To date, reports of confusion and error between Children's Tylenol and the currently marketed Children's Advil have not been reported to the Agency. Therefore, we believe the inclusion of "Allergy Sinus" on the Children's Advil product will help distinguish it from the Children'sTylenol product line, specifically Children's Tylenol Sinus and Children's Tylenol Allergy.

2. [redacted]

2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, "Children's Advil Allergy Sinus". However, DMETS does not recommend the use of the proprietary name

B. DMETS recommends implementation of the label and labeling recommendations outlined in section III of this review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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ON ORIGINAL

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/s/

Nora L. Roselle
11/12/03 01:08:46 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
11/12/03 01:14:50 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/12/03 02:21:54 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
11/12/03 02:28:18 PM
DRUG SAFETY OFFICE REVIEWER

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
9201 Corporate Boulvard
Rockville, MD 20850

To:	David Smith, PhD	**From:**	Ms. Jane A. Dean, RN, MSN
Fax:	973-660-8698	**Fax:**	301-827-2531
Phone:	973-660-6806	**Phone:**	301-827-2090
Pages:	2 (including cover page)	**Date:**	11-21-2003
Re:	NDA 21-587 – Comments on CMC issues		

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

• **Comments:** Dear David, the following comments pertain to CMC issues:

1. Please provide data to support your claim that antimicrobial activity remains effective when sodium benzoate contained in the drug product is at 80% of the initial concentration.
2. Please provide justification for not testing unspecified degradants and microbial limits at drug product release.
3. [redacted] failed to contain any information on the [redacted] that will be used for the [redacted] Please provide a statement that the [redacted] for the [redacted] meets the food additive regulations.
4. The limit for unspecified individual degradant related to chlorpheniramine as NMT [redacted] based on ICH threshold for qualification is not acceptable. The limit should be established based on ICH threshold for identification, which for chlorpheniramine related degradant with maximum daily dose of 8 mg is 20 µg or [redacted] The limit of total unspecified degradants should be revised accordingly.
5. Accuracy of the amount delivered by using the proposed dosing cup should be validated. Instruction how to use the cup should be provided as a part of the labeling. Please also submit the validation result for review.

6. Reduced stability testing proposed at second, third year and each year thereafter is not acceptable at this time. You may request reduced stability testing when sufficient stability data are available.
7. With the submission of ——— room temperature stability data on only one batch (clinical batch) and ——" room temperature stability data on 3 full scale NDA batches, Berry Flavors, the proposed expiration period of ——— is not acceptable. Please provide additional stability data for review.

If you have any questions, please feel free to call me at 301-827-2536.

Sincerely,

Jane Dean
Project Manager

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/s/

Jane Dean
11/21/03 06:13:23 PM

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Division of OTC Drug Products Labeling Review

NDA 21-587

Submission Dates: August 23, 2003
October 22, 2003
Review Date: November 4, 2003

Applicant:

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Applicant's Representative:

Lauren Quinn
Associate Director, Regulatory Affairs
973-660-6167

Drug:

Children's Advil® Allergy, and [redacted]

(ibuprofen 100 mg/5 mL, pseudoephedrine hydrochloride 15 mg/5 mL, chlorpheniramine maleate 1 mg/5 mL Suspension)

Pharmacologic Category:

pain reliever/fever reducer/nasal decongestant/ antihistamine

Submitted:

1 fl oz, [redacted] and 8 fl oz carton and container labels for both berry flavor and [redacted] for each Children's Advil® Allergy and [redacted] product

Background:

Chlorpheniramine maleate has been included as an active ingredient in the final monograph for OTC antihistamine drug products since December 9, 1992. On April 18, 2002, the Agency approved pseudoephedrine HCl and ibuprofen as a nasal decongestant and pain reliever/fever reducer combination for Advil® Cold and Sinus Caplets (NDA 21-373). On August 21, 2002, the Agency proposed inclusion of ibuprofen in the OTC internal analgesic monograph (67 FR 54139). On December 19, 2002, the Agency approved chlorpheniramine maleate, pseudopehedrine HCl, and ibuprofen as an antihistamine, nasal decongestant, and pain reliever/fever reducer combination for adults and children 6 years and older as Advil® Allergy and Sinus Caplets (NDA 21-441). On August 23, 2003, sponsor submitted labeling for this review under the brandname

Children's Advil® Allergy Sinus Suspension. On October 22, 2003, sponsor amended this submission to change the product brandname to Children's Advil® Allergy. Currently, the sponsor seeks approval for a children's liquid formulation of the same 3 active ingredients under the brandnames of Children's Advil® Allergy Suspension, and as [redacted] for children 6 to under 12 years of age.

Reviewer's Comment: Reviewer recommended additions are identified by red shaded text and deletions are identified by "strike out."

I. CARTON LABELING

[redacted]

44 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

3 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
9201 Corporate Boulvard
Rockville, MD 20850

To: David Smith, PhD	**From:** Ms. Jane A. Dean, RN, MSN
Fax: 973-660-8698	**Fax:** 301-827-2531
Phone:973-660-6806	**Phone:** 301-827-2090
Pages: 3 (including cover page)	**Date:** 9-3-2003
Re: NDA 21-587 Biopharm Information Request	

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

• **Comments:** Dear David, the following information request will be coming to you in the mail. I am faxing it to you ahead of time to facilitate the timeliness of a response. If you have any questions, please feel free to call me at 301-827-2536.

Sincerely,

Jane Dean
Project Manager

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/s/

Jane Dean
9/3/03 04:18:35 PM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-587

INFORMATION REQUEST LETTER

Wyeth Consumer Healthcare
Attention: David Smith, PhD
Director, Regulatory Affairs
Five Giralda Farms
Madison, NJ 07940

Dear Dr. Smith:

Please refer to your April 23, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Children's Advil® Allergy Sinus/ [redacted] (ibuprofen 100 mg/pseudoephedrine HCl 15 mg/chlorpheniramine maleate 1mg/5 ml suspension).

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

1. Please report the 90% CI of the ratio of the mean (based on log transformed data) of pharmacokinetic parameters of ibuprofen, pseudoephedrine and chlorpheniramine obtained between adult and pediatric population in Study AR -00- 03.

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

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
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/

Carmen DeBellas
9/3/03 03:20:19 PM

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NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **21-587**

Trade Name: **Children's Advil® Allergy Sinus/**
Generic Name: **ibuprofen 100 mg/pseudoephedrine HCl 15 mg/ chlorpheniramine maleate 1 mg/5 ml suspension**
Strengths: **ibuprofen 100 mg/pseudoephedrine HCl 15 mg/ chlorpheniramine maleate 1 mg/5 ml suspension**
Applicant: **Wyeth Consumer Healthcare**

Date of Application: **April 23, 2003**
Date of Receipt: **April 24, 2003**
Date of Filing Meeting: **June 6, 2003**
Filing Date: **June 22, 2003**
Action Goal Date (optional): **December 17, 2003**
User Fee Goal Date: **February 24, 2004**

Indication(s) requested: **Pain reliever/nasal decongestant/antihistamine for the relief of symptoms associated with allergic rhinitis and the common cold**

Type of Application: Original (b)(1) NDA ____X____ Original (b)(2) NDA _____
(b)(1) Supplement _____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S ___X_____ P _____
Resubmission after a withdrawal? ___N_____ Resubmission after a refuse to file? ____N____
Chemical Classification: (1,2,3 etc.) ___3_____
Other (orphan, OTC, etc.) ___OTC___

User Fee Status: Paid ___X_____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: **YES**
User Fee ID # **4500**
Clinical data? YES ___X___ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? **NO**

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? **n/a**

Is the application affected by the Application Integrity Policy (AIP)? **NO**

- Does the submission contain an accurate comprehensive index? **YES**
- Was form 356h included with an authorized signature? **YES**
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? **YES**
- If an electronic NDA, does it follow the Guidance? **YES**
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  All parts of the submission

- If in Common Technical Document format, does it follow the guidance? **n/a**
- Is it an electronic CTD? **NO**
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? **n/a**
- Patent information included with authorized signature? **YES**
- Exclusivity requested? **YES**
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? **YES**
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure information included with authorized signature? **YES**
  (Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES**

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES**
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? **YES**
- List referenced IND numbers: **IND 63,999**
- End-of-Phase 2 Meeting(s)? **NO**
  If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? **YES** Date(s) **1/8/03**
  If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? **NO**
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? **NO**
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? **n/a**
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? **n/a**

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? **n/a**
- Has DOTCDP been notified of the OTC switch application? **n/a**

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **n/a**

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **YES**
  If no, did applicant submit a complete environmental assessment? **n/a**
  If EA submitted, consulted to Nancy Sager (HFD-357)? **n/a**
- Establishment Evaluation Request (EER) submitted to DMPQ? **YES**
- If parenteral product, consulted to Microbiology Team (HFD-805)? **n/a**

If 505(b)(2) application, complete the following section: **n/a**

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

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

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

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO

  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO

  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    YES, IND # _____ NO

    OR
    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

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ATTACHMENT

MEMO OF FILING MEETING

DATE: **June 6, 2003**

BACKGROUND: **This is a pediatric formulation of the triple combination of ibuprofen, pseudoephedrine and chlorpheniramine in a suspension. The adult formulation (NDA 21-441) was approved on December 19, 2002, jointly reviewed by the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550 and the Division of Over-the-Counter Drug Products, as will this product.**

ATTENDEES:

Dennis Bashaw, PharmD	**HFD-880**
Carolyn Yancey, MD	**HFD-550**
Curtis Rosebraugh, MD, MPH	**HFD-560**
John Smith, PhD	**HFD-830**
Nancy Halonen, RN	**HFD-550**
Terri Rumble, RN	**HFD-105**
Tapash Ghosh, PhD	**HFD-880**
Brian Harvey, MD	**HFD-105**
Jonca Bull, MD	**HFD-105**
Christina Fang, MD	**HFD-550**
Elaine Abraham, RPh	**HFD-560**
Andrea Leonard-Segal, MD	**HFD-560**
Marina Chang, RPh	**HFD-560**
James Witter, MD PhD	**HFD-550**
Lee Simon, MD	**HFD-550**
Jane Dean, RN, MSN	**HFD-550**

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	**Christina Fang**
Secondary Medical:	**Daiva Shetty**
Statistical:	**Stan Lin**
Pharmacology:	**Maria Rivera**
Statistical Pharmacology:	**n/a**
Chemist:	**Bart Ho**
Environmental Assessment (if needed):	**n/a**
Biopharmaceutical:	**Tapash Ghosh**
Microbiology, sterility:	**n/a**
Microbiology, clinical (for antimicrobial products only):	**n/a**
DSI:	**n/a**
Regulatory Project Manager:	**Jane Dean/Elaine Abraham**
Other Consults:	**n/a**

Per reviewers, are all parts in English or English translation? **YES**

CLINICAL FILE __X__ REFUSE TO FILE ____

- Clinical site inspection needed: **YES**
- Advisory Committee Meeting needed? **NO**
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **n/a**

CLINICAL MICROBIOLOGY **n/a**

STATISTICS FILE __X__ REFUSE TO FILE ____

BIOPHARMACEUTICS FILE __X__ REFUSE TO FILE ____

- Biopharm. inspection needed: **YES**

PHARMACOLOGY FILE __X__ REFUSE TO FILE ____

- GLP inspection needed: **NO**

CHEMISTRY FILE __X__ REFUSE TO FILE ____

- Establishment(s) ready for inspection? **YES**
- Microbiology **n/a**

ELECTRONIC SUBMISSION: **YES**

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

__X__ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

__X__ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.

2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Jane A. Dean, RN, MSN
Regulatory Project Manager, HFD-**550**

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/s/

Jane Dean
7/25/03 04:14:29 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*:	FROM:
Diane Tesch, RNP/Karen Storms **Division of Scientific Investigations** **HFD-47, MPN 1** **7520 Standish Pl., Rm. 103**	**Dr. Christina Fang/Jane A. Dean, RN, MSN x72536** **DAAODP, HFD-550**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 15, 2003		**21-587**	**NDA original submsiion**	**April 23, 2003**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Children's Advil Allergy Sinus/Dimetapp Allergy & Sinus Ibuprofen 100 mg/Pseudoephedrine 15 mg/Chlorpheniramine 1 mg/ 5ml	**Standard**	**3S**	**October 6, 2003**

NAME OF FIRM: **Wyeth Consumer Healthcare**

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

X CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Per Dr. Fang's request, please inspect the following clinical site:**

1. **For Study # AR-00-04 (Children's Advil AllergySinus Suspension Multiple-Dose Safety Study in children 6 to <12 Years of Age with Symptoms Consistent with Allergic Rhinitis):**
   - **Paul Chervinsky, MD, Northeast Medical Research Assoc., Inc., 49 State Rd., Watuppa Bdg, North Dartmouth, MA 02747**

2. **For the same study listed above, one of the following three clinical sites needs to be inspected, please:**
   - **Nathan Segall, MD, 175 Country Club Dr., Building 100-A, Stockbridge, GA 30281**
   - **Grant C. Olson, MD Clinical Research Centers of Colorado, PC, 1667 Cole Blvd., Bdg. 19, #205, Lakewood, CO 80401-3300**
   - **Ned Rupp, MD, Radiant Research Inc., 1879 Savage Rd., Charleston, SC 29407**

If you need any additional information, please contact the **Project Manager, Jane A. Dean, RN, MSN at x 72536. Thank you.**

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Dr. Christina Fang/Jane A. Dean, RN, MSN x72536	X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Dianne Tesch
7/30/03 02:53:01 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*:	FROM:
Dr. Viswanathan **Division of Scientific Investigations** **HFD-48, MPN 1** **7520 Standish Pl., Rm. 151**	**Dr. Christina Fang/Jane A. Dean, RN, MSN x72536** **DAAODP, HFD-550**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 15, 2003		**21-587**	**NDA original submsiion**	**April 23, 2003**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Children's Advil Allergy Sinus/ **Ibuprofen 100 mg/Pseudoephedrine 15 mg/Chlorpheniramine 1 mg/ 5ml**	**Standard**	**3S**	**October 6, 2003**

NAME OF FIRM: **Wyeth Consumer Healthcare**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Per Dr. Fang's request, please inspect the following clinical site:**

1. **For Study # AR-00-02 (A Three-Way Crossover Bioavailability/Food Effect Study of a Suspension Containing Ibuprofen 100 mg, Pseudoephedrine Hydrochloride 15 mg, and Chlorpheniramine Maleate 1 mg/5 ml):**

2. **For Study # AR-00-03 (A Bioavailability Study of a Suspension Formulation of Ibuprofen/Pseudoephedrine Hydrochloride/Chlorpheniramine Maleate in Children 6 to <12 Years of Age with Symptoms Consistent with Allergic Rhinitis):**

If you need any additional information, please contact the Project Manager, Jane A. Dean, RN, MSN at x 72536. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Dr. Christina Fang/Jane A. Dean, RN, MSN x72536	X MAIL ☐ HAND
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Dianne Tesch
7/30/03 02:49:11 PM

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

REQUEST FOR CONSULTATION

TO (Division/Office):
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
PKLN Rm. 15B-23

FROM:
Jane A. Dean, RN, MSN, Project Manager HFD-550
X72536

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 11, 2003		21-587		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Children's Advil Allergy Sinus/ [redacted] mg/Pseudoephedrine 15 mg/Chlorpheniramine 1 mg per 5 ml (OTC)	Routine	3/S	October 6, 2003 (NDA Target Review Date)

NAME OF FIRM: **Wyeth Consumer Healthcare**

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

PDUFA DATE: **February 22, 2004**
ATTACHMENTS: Draft Proposed Labeling and Carton Labels

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Jane A. Dean, RN, MSN, HFD-550 x72536	X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jane Dean
2/13/04 05:05:59 PM
ODS Consult #: 03-0203 Review completed 11-12-03 and in DFS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-587

Wyeth Consumer Health
Attention: David Smith, PhD
Director, Regulatory Affairs
Five Giralda Farms
Madison, NJ 07940

Dear Dr. Smith:

Please refer to your April 23, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Children's Advil® Allergy Sinus/ [redacted] (ibuprofen 100 mg/pseudoephedrine HCl 15 mg/chlorpheniramine maleate 1mg/5 ml suspension).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on June 22, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. **Biopharmaceutics**: You are advised to report 90% CI of the ratio of the mean (based on log transformed data) of pharmacokinetic parameters of ibuprofen, pseudoephedrine and chlorpheniramine obtained between adult and pediatric population in Study AR -00- 03.

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

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

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

Sincerely,

{See appended electronic signature page}

Lee S. Simon, MD
Director
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/

Lee Simon
6/27/03 05:26:42 PM

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ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-587

Wyeth Consumer Healthcare
Attention: David S. Smith, PhD
Director, Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Dr. Smith:

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

Name of Drug Product:	Children's Advil® Allergy Sinus/ [redacted] (ibuprofen 100 mg/pseudoephedrine HCl 15 mg/chlorpheniramine maleate 1 mg/5 ml) Suspension
Review Priority Classification:	Standard
Date of Application:	April 23, 2003
Date of Receipt:	April 24, 2003
Our Reference Number:	NDA 21-587

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 22, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 22, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
9201 Corporate Boulevard
Rockville, Maryland 20850

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

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R. Ph.
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

APPEARS THIS WAY
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/s/

Carmen DeBellas
5/5/03 02:43:28 PM

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	January 8, 2003
TIME:	3:30pm – 4:30pm
LOCATION:	S300
APPLICATION (DRUG):	IND 63,999 (Children's Advil Allergy Sinus suspension– ibuprofen 100mg/pseudoephedrine 15mg/chlorpheniramine 1mg per 5ml)
SPONSOR:	Wyeth Consumer Healthcare
TYPE OF MEETING:	PreNDA telecon with sponsor
MEETING CHAIR:	James Witter, MD, PhD
MEETING RECORDER:	Ms. Jane A. Dean, RN, MSN

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name of FDA Attendee	Title	Division Name & HFD#
1. Lee S. Simon, MD	Division Director	ODE V/DAAODP, HFD-550
2. James Witter, M.D., PhD	Medical Officer Team Leader	ODE V/DAAODP, HFD-550
3. Christina Fang, MD	Medical Reviewer	ODE V/DAAODP, HFD-550
4. Dennis Bashaw, PharmD	Biopharm Team Leader	DPS/DPEIII, Hfd-880
5. Carmen DeBellas, RPh	Chief Project Manager	ODE V/DAAODP, HFD-550
6. Terri Rumble, RN	Associate Director Regulatory Affairs	ODE V
7. Andrea Leonard-Segal, MD	Medical Team Leader	ODE V/DOCDP, HFD-560
8. Elaine Abraham, RPh	Project Manager	ODE V/ DOCDP, HFD-560
9. David Hilfiker, MS	Chief Project Manager	ODE V/ DOCDP, HFD-560
10. Daiva Shetty, MD	Medical Reviewer	ODE V/ DOCDP, HFD-560
11. Michele Jackson, PhD	IDS Reviewer	ODE V/ DOCDP, HFD-560
12. John O'Malley	Information Technology Specialist	ODE V
13. Vispi Bhavnagri, PhD	Chemistry Reviewer	OPS/ONDS/HFD-830
14. Robert Shibuya	Pharmacologist	DSI
15. Jane A. Dean, RN, MSN	Project Manager	ODEV/DAAODP, HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Roger Berlin, MD	President, Global Scientific Affairs	Wyeth Consumer Healthcare
2. Stephen Cooper, DMD, PhD	Sr. VP, Global Clinical and Medical Affairs	Wyeth Consumer Healthcare
3. Sharon Heddish	VP, Regulatory Affairs Worldwide	Wyeth Consumer Healthcare
4. Suman Wason, MD, MBA	Sr. Director, Clinical Research	Wyeth Consumer Healthcare
5. Elizabeth Ashraf, PhD	Sr. Director, Medical Communications	Wyeth Consumer Healthcare
6. David Smith	Director, Regulatory Affairs	Wyeth Consumer Healthcare

External Attendee	Title	Sponsor/Firm Name
7. Michael Chen	Assistant Director, Biostatistics	Wyeth Consumer Healthcare
8. Lauren Quinn	Associate Director, Regulatory Affairs	Wyeth Consumer Healthcare
9. Julia Kim, PharmD	CMC	Wyeth Consumer Healthcare
10. Paul Butkereit	Medical Communications	Wyeth Consumer Healthcare
11. Damien Hirsch	Safety and Surveillance	Wyeth Consumer Healthcare

General Comments:

The Agency asked the sponsor to clarify which indication they wanted for their product. The sponsor stated that they were going for the same indication as was in the adult version of this product (NDA 21-441); that is, for the temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold. Although not required, the sponsor was encouraged to perform efficacy studies at lower doses of the combination in the 6 – 12 age group. It was noted that the studies conducted in adults established that a lower dose was as effective as the higher dose. It would be important to determine whether this also holds true for children.

A controlled design for the safety study would generate data that is easier to evaluate. Clinical trial data are not reliably interpretable without the controls.

The Sponsor should provide all safety data available (i.e. global safety data, literature reports) about the concurrent use of these three ingredients in the pediatric population.

The sponsor should adequately power any efficacy and safety studies that they perform to support the NDA.

QUESTION 1 (labeling):

Wyeth Consumer Healthcare proposes to use the proprietary names Advil® Allergy Sinus Suspension and [redacted] With respect to the [redacted] brand, product currently marketed under the [redacted] brand include:

Product Name	Form	IBU	APAP	PSE	DM	GU	BROM	CHLOR	PHY	PECTIN
Liquids										
	Syrup			15mg/ 5mL			1mg/ 5mL			
	Syrup			15mg/ 5mL	5mg/ 5mL		1mg/ 5mL			
	Syrup			15mg/ 5mL	7.5mg/ 5mL					
	Syrup		160mg/ 5mL	15mg/ 5mL	5mg/ 5mL		1mg/ 5mL			
	Syrup		160mg/ 5mL	15mg/ 5mL	5mg/ 5mL					
	Suspension	100mg/5 mL		15mg/ 5mL						
	Liquid			7.5mg/ 0.8mL						
	Liquid			7.5mg/ 0.8mL	2.5mg/ 0.8mL					
	Tablet			120mg						
	Tablet		325mg					2mg	5mg	

Product Name	Form	IBU	APAP	PSE	DM	GU	BROM	CHLOR	PHY	PECTIN
	Caplet			30mg	10mg	200mg				
	Lozenge									19mg
	Lozenge									19mg

Legend:
IBU = IBUPROFEN APAP = ACETAMINOPHEN PSE = PSEUDOEPHEDRINE
DM = DEXTROMETHORPHAN GU - GUAIFENESIN BROM = BROMPHENIRAMINE
CHLOR = CHLORPHENIRAMINE PHY = PHENYLEPHRINE

There is no product that presently contains an analgesic, antihistamine and nasal decongestant which would be confused [redacted] and therefore, this name should be acceptable. Does the Agency concur?

FDA Response: *The Agency is concerned that consumers may be confused when a single brand name can have a variety of different ingredients. It is appropriate to try to minimize the potential for concurrent use of products that contain the same or similar ingredients by selecting a brand name that conveys as much as possible about the contents of the product.*

The Agency cannot provide comment on the name of the product at this time. We do have some concerns regarding the ability of consumers to understand that the product contains an internal analgesic. The name has generally not been associated with the presence of an internal analgesic. If the Brand name is used, the sponsor should bear in mind that consumers must be able to determine that there is an internal analgesic in this triple combination product. Additionally, because some of the products contain acetaminophen, the consumer should be able to discern which internal analgesic is in the product they are buying. Thus, the principal display panel should include language that adequately conveys this information.

The name will require review by the Office of Drug Safety. This review cannot begin until the application is submitted.

QUESTION #2 (Clinical Data/Statistical Analysis):

The clinical development plan and proposed statistical analysis are presented in this briefing document. This same approach was used for NDA 21-441 (Advil Allergy Sinus Tablets) and found to be acceptable. Does the Agency concur with the proposed statistical analysis?

FDA Response: *Exclusion criteria for the safety study should be as few as ethically possible when a product is being assessed for safety for the OTC marketplace. The sponsor stated that the study was already conducted. The usefulness of the information from this study will be determined at the time of review. Of equal concern are the anecdotal reports of acute renal failure in dehydrated pediatric patients associated with the use of ibuprofen. Warnings may need to be included on the label to address this potential complication.*

NOTE: Wyeth referred to the protocol submitted to the IND in April 2002 and stated that they did not receive any FDA comments on its content. FDA suggested that Wyeth make more of an effort to highlight protocols for studies that are considered essential to a future NDA approval. Before

starting the study, Wyeth could have placed a call to FDA to inquire about comments on the study design. Because the study is now complete, FDA may consider the results in the NDA review but labeling for the product may prove to be difficult for the general OTC population because of limits placed on the population that was enrolled in the study.

QUESTION #3 (Item 8H – Integrated Summary of Safety):

1. Wyeth Consumer Healthcare plans to summarize the spontaneous adverse drug experience data by adhering to the format for the ICH PSUR, sections 6-9. Although there are no currently marketed products containing ibuprofen/pseudoephedrine/chlorpheniramine, this safety review will include reports involving patients who concurrently took all three active drugs. This same approach was used for NDA 21-441 (Advil Allergy Sinus Tablets) and found to be acceptable. Reports will be extracted from two sources:
   - the sponsor's own spontaneous adverse event database for reports received between September 15, 2001 and September 30, 2002 (the "cut-off" date);
   - from the FDA's Adverse Event Reporting System (AERS) for the time period April 1, 2001 through first quarter 2002 (currently the latest update available).

   Does the Agency find this approach acceptable?

FDA Response: *See below.*

2. Similarly, Wyeth Consumer Healthcare plans to summarize the overdose data involving patients who concurrently took all three active drugs. Reports will be extracted from two sources:
   - The sponsor's own spontaneous adverse event database and the American Association of Poison Control Centers (AAPCC) starting from December 31, 2001 (cross-reference NDA 21-441 for prior dates).

   Does the Agency agree with this proposal?

FDA Response: *See below.*

3. For the quarterly safety updates Wyeth Consumer Healthcare plans to submit the following:
   - for the marketed, combination product containing ibuprofen, pseudoephedrine, and chlorpheniramine summaries of expedited reports received from spontaneous sources starting October 1, 2002;
   - any new overdose reports received since October 1, 2002 in the sponsor's own spontaneous adverse event database describing patients who concurrently took all three active drugs;
   - when available from AAPCC, an update of the overdose data involving patients who concurrently took all three active drugs;
   - Any new literature reports involving patients who concurrently took all three active drugs.

   Does the Agency have any comments regarding the safety updates?

FDA Response: *In addition to providing the safety data discussed above, the sponsor should update the safety information for the individual ingredients and for the ibuprofen/pseudoephedrine combination and chlorpheniramine /pseudoephedrine combination products. The potential for renal toxicity in dehydrated children who take ibuprofen-containing products (e.g., children with fever) should be evaluated. The case descriptions should be submitted for all cases of serious adverse events and drug overdose. Overdose data should also include FDA's post-marketing surveillance safety database. Safety data should be provided and summarized up to 6 months prior*

to the filing of the NDA. Quarterly safety updates should start six months prior to filing of the NDA.

QUESTION #4 (Pediatric Exclusivity):

WCH submitted a request on August 8, 2002 for the Agency to request studies to fulfill the pediatric exclusivity requirements. Is the Agency in agreement that the clinical program will meet those requirements?

FDA Response: *The initial response from the Pediatric group was that the sponsor is not eligible for exclusivity because ibuprofen has already received it twice. We will provide a response in a separate letter.*

QUESTION #5 (Electronic Submission):

Wyeth Consumer Healthcare (WCH) is planning to submit a fully electronic NDA that is compliant with the current CDER guidelines for electronic NDA submissions. We will follow the Guidance For Industry "Providing Regulatory Submissions in Electronic Format – NDA's" (January 1999). A full summary of the specifications follows.
In accordance with this guidance:

- An archival copy will be submitted in fully electronic format
- The paper review copy will exclude the following items:
  1. CMC methods validation reports
  2. Clinical study report appendices 16.1.3 to 16.4 (as defined by ICH Guidelines)
  3. Items 11 & 12
- Item 11 will contain two sections:
  1. SAS datasets (CRF and derived data for studies submitted under Item 8D; CRF data plus any plasma concentration and derived PK data for studies submitted under Item 6.)
  2. Patient profiles (to match submitted CRFs)
- Item 12 will contain images of CRFs for SAEs and discontinuations due to AEs.

Due to the need for 100% quality assurance and verification during the scanning process, full-text indexing will not be provided for scanned images in the appendices of the clinical study reports and the CMC sections.

Reviewer's Aids

(Please note that the reviewer's aids are different than the paper review copy, which will be provided as described above).

The only reviewer aid that will be provided is a labeling reviewer's aid. For the labeling reviewer's aid, a copy of the draft labeling text ("Proposed Text") will be provided in a Word format on a separate diskette from the electronic submission, per the FDA Guidance on Electronic Submissions. In addition to the Word file, a copy of the labeling in the form of readers or "mock-ups" will also be provided in a separate binder.

Since we will be following the 1999 Guidance on Electronic Submissions, we do not intend to provide any additional Reviewer's aids. However, if we are required to provide review tools over and above those outlined in the guidance, such requests can be more easily accommodated if it they are identified now.

Is the Agency in agreement with this proposal?

FDA Response: *Yes, as long as the guidance for electronic submissions is followed.*

Additional Comments (CMC issues):

a) *For the flavors, please provide composition and CFR citation or relevant safety information for each ingredient contained in the flavors. The information may be included in the NDA or cross-referenced to DMFs where this information can be found.*

b) *In addition to the tests performed for the clinical studies (submitted in the original IND), the following tests and their acceptance criteria should be included in the regulatory specification of the drug product: Uniformity of Dosage Units (ICH Q6A3.3.2.2), Deliverable volume (USP <698>), and redispersibility (ICH Q6A 3.3.2.2(J)). Identification tests should be specific for the drug substances. Identification solely by the retention time of the major peaks in the HPLC chromatogram is not adequate. If the ID test is not specific, two identification tests are required. Please refer to ICH Q6A, Section 3.2.2 b), Identification testing to establish the identity of the drug substance in the drug product.*

c) *How will the dose be measured for administration? If a cup is being provided, it should be calibrated using the drug product (or vehicle).*

d) *Acceptance criteria for degradation products should include each specified, any unspecified, and total degradation products. Refer to ICHQ3B Guidance on Impurities in New Drug Products. .*

e) *An expiration period is determined by the amount of stability data submitted to the NDA. The amount of data to be included in the submission, as stated on pages 36 and 37 of the meeting package, do not appear to support the proposed expiration period of 24 months.*

To aid the chemists with their evaluation, they would like the methods and validation information submitted in one package. Furthermore, the data needs to be reorganized to make it more readable for the reviewers.

Minutes Preparer: Jane A. Dean, RN, MSN

Chair Concurrence: James Witter, MD, PhD

Drafted by: J. A. Dean
Initialed by: J. Witter, MD, PhD
Final: March 6, 2003

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/s/

Lee Simon
3/13/03 02:09:18 PM

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