CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-373

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

K1.1A

K1.1A

N21373

N21373

REC.
5/11/02
2:25PM

ACTION PACKAGE

NDA 21-373

CHILDREN'S ADVIL COLD SUSPENSION

BY WYETH CONSUMER HEALTHCARE
(Originally Whitehall Robins)

Receipt Date: June 18, 2001
User Fee Goal Date: April 18, 2001

Project Manager: Babette Merritt, OTC (HFD-560), Team 1

Number of Pages Redacted 4

❖❖❖

Confidential,
Commercial Information

MEMORANDUM

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

DATE: April 2, 2002

TO: Carmen Debellas, Supervisory Consumer Safety Officer
Division of Antiinflammatory, Analgesics, and Ophthalmic Drug Products, HFD-550

FROM: David Hilfiker, Supervisory Consumer Safety Officer
Division of Over the Counter Drug Products, HFD-560

SUBJECT: Transfer of NDAs 21-373 and 21-374
Advil Cold and Sinus ' ——— Liquigels

In contradiction to the ORM policy of placing administrative responsibility of NDAs within the Division that reviews the principal clinical research activity of the drug, this memorandum documents that the Division of Over the Counter Drug Products has agreed to accept primary responsibility for the oversight of the review and action for these NDA applications. If you do not concur, please include the reason as a signature comment. If you have any questions, call me at 301-827-2265.

APPEARS THIS WAY
ON ORIGINAL

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/s/

David Hilfiker
4/2/02 02:26:18 PM
CSO

Carmen DeBellas
4/3/02 12:43:06 PM
CSO

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Wyeth Consumer Healthcare
Children's Advil Cold Suspension

NDA 21-373
4/18/2001

ITEM 14: PATENT CERTIFICATION

In the opinion and to the best knowledge of Wyeth Consumer Healthcare, there are no patents that claim the drug or drugs on which the investigations that are relied upon in this application were conducted, or that claim a use of such drug or drugs.

David S. Smith, PhD
Director, Regulatory Affairs

EXCLUSIVITY SUMMARY for NDA # 21-373 SUPPL # _____

Trade Name Advil Cold/ ~~~
Generic Name ibuprofen/pseudoephedrine
Applicant Name Wyeth Consumer Healthcare HFD- 560
Approval Date April 18, 2002

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 /_X_/ NO /___/

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

3 years

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

YES /_X_/ NO /___/

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 /_X_/ NO /___/

If yes, NDA # 21-128 Drug Name Children's Motrin Cold

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 /___/

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 /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

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

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 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 /___/ 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 /___/

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

Investigation #1, Study # _____

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	YES /___/	NO /___/
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 /___/

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 #__, Study # _____

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 # _____ YES /___/ ! 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?

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: _____

_____

_____

(see appended electronic signature page)
Signature of Preparer

Date

Title:_____

_____
Signature of Office or Division Director

_____
Date

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
4/18/02 03:59:12 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-373

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Attention: David Smith, Ph.D.
Director, Regulatory Affairs

Dear Dr. Smith:

Please refer to your new drug application (NDA) submitted June 15, 2001 and approved on April 18, 2002, for Children's Advil Cold —— Suspension.

In the April 18, 2002, approval letter, the first paragraph is hereby revised to read as follows:

> Please refer to your new drug application (NDA) dated June 15, 2001, received June 18, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Children's Advil Cold (100 mg per 5 ml ibuprofen and 15 mg per 5 ml pseudoephedrine hydrochloride) Suspension.

If you have any questions, contact Elaine Abraham, Project Manager, at (301) 827-2222.

Sincerely yours,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Division of Over-The-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Charles Ganley
4/29/02 10:51:59 AM

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Division of Over-the-Counter Drug Products
Labeling Review

NDA #: 21-373

Submission Date: 07/18/01
01/16/02 and 3/19/02
Review Date: 02/04/02 and 3/22/02

APPLICANT'S REPRESENTATIVE: Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

DRUG: Children's Advil Cold Suspension
(Ibuprofen 100 mg and Psuedoephedrine HCl 15 mg per 5 mL)

PHARMACOLOGIC CATEGORY: Pain reliever and fever reducer

SUBMITTED: Draft carton and container labels for 4 ← fl. oz.

BACKGROUND:

Reference is made to the electronic submissions dated 7/18/01 for Children's Advil Cold Suspension carton and container labels for 4 ——fl. oz. Reference is also made to the amended submission dated 1/16/02 in which the sponsor included the design of a dosing cup and related labeling statements. The submissions contain draft labeling in Drug Facts format (§ 201.66). The review of the content for the "Drug Facts" is based on the 1/16/02 submission. The sponsor amended the submission with labeling for a new design of the Principal Display Panel for the product on March 19, 2002. It also noted that the change is an artwork change only; all other aspects of the packaging (sizes, shape, dosing cup Drug Facts) remain unchanged.

REVIEWER'S COMMENT:

I. Carton:
   A. Principal Display Panel:
      1. "New" - the sponsor will need to remove this promotional flag six months following introduction into the marketplace. This flag is not on the PDP of the new design submitted on 3/19/02.

      2. We encourage the inclusion of the established names and concentrations as part of the statement of identity.

   B. Drug Facts Labeling

1. Active ingredients: - we encourage the use of "teaspoon" instead of "tsp", if space allows.

2. Warnings

a. Ask a doctor before use if the child has, third bullet: - for clarity, we encourage the revision of this bullet from '

b. Stop use and ask a doctor if: - combine the 3rd bulleted statement (i.e., "fever or pain gets worse, or lasts for more that 3 days ") and the 4th bulleted statement (i.e.,"cold, sinus and flu symptoms do not improve within 7 days") into one bulleted statement (i.e., " • fever, pain or nasal congestion gets worse or lasts for more than 3 days"). There is insufficient data to support "7 days" duration of use because there was limited exposure in patients with fever and only 27 subjects took this combination product for 7 days in the sponsor's safety trial.

3. Directions: -

   a. Delete the second bullet (i.e., "do not give for more than 2 days for sore throat, for more than 3 days for fever or pain, or for more than 7 days for cold, sinus and flu symptoms"). There are too many conditions to this statement that could cause confusion to the consumers. Also the time frame for stop using this product for cold, sinus and flu symptoms has been revised to be only 3 days for both fever and cold symptoms.

   b. ——— third bullet (i.e., Shake well before using).

   c. The sponsor added, "measure only with dosing cup provided. Dosing cup to be used with Children's Advil Cold Suspension only. Do not use with other products. Dose lines account for product remaining in cup due to thickness of suspension". This statement is the same statement approved in for the sponsor's single ingredient suspension (Ibuprofen, NDA 20-589), except the mention of the color of the dosing cup.

4. Question or comments: - we recommend that the days of the week and times of the day when a person is available to respond to questions also be included.

II. Container Label: - Not satisfactory. See comment for carton label 3 (b).

III. Others:

a. Allergy Alert statements: - The sponsor's submission provided data showing a high proportion of the AE cases reported for the combination product involved allergic reactions. Currently we are addressing the allergy alert warning statement through the OTC drug monograph proposed rulemaking processes.

b. Warnings: - The statements "give with food or milk if stomach upset occurs" in *When using this product* subsection and "stomach pain or upset gets worse or lasts" in *Stop use and ask a doctor if* subsection need to be re-evaluation for better phrasing in the future class labeling changes.

c. The labeling format and text are in compliance with § 201.66.

RECOMMENDATION:

I. Inform the sponsor that the following changes to the carton labels must be committed prior to the issuance of an action letter.

2. Directions: -

II. Also inform the sponsor that we encourage it to further revise the label as follows:-

1. Statement of identity - include the established names and concentrations.

2. Active Ingredients - use of "teaspoon" instead of "tsp".

3.

Bettie Ryland, IDS

Concur
Marina Chang, R. PH.
Team Leader

Concur
Linda Hu, MD
Medical Officer

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/s/

Elizabeth Ryland
4/3/02 02:15:48 PM
INTERDISCIPLINARY

Linda Hu
4/9/02 03:10:08 PM
MEDICAL OFFICER

Marina Chang
4/9/02 05:00:07 PM
INTERDISCIPLINARY

Division of Over-the-Counter Drug Products
Addendum Labeling Review

NDA #: 21-373

Submission Date: 4/9, 10 and 11/02 (via e-mail)
4/12/02
Review Date: 4/10, 11 and 17/02

APPLICANT'S REPRESENTATIVE: Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

DRUG: Children's Advil Cold Suspension
(Ibuprofen 100 mg and Psuedoephedrine HCl 15 mg per 5 mL)

PHARMACOLOGIC CATEGORY: Pain reliever and fever reducer and nasal decongestant

SUBMITTED: Draft carton and container labels for 4 fl. oz., Grape Flavor

Reviewer's Comments: Sponsor has complied with the Agency's recommendations, dated 4/3 (via fax), 9 and 11(via telephone communication). The color mock-up carton label and container labels submitted on 4/12/02 are satisfactory.

Recommendations: The application is approvable based on the carton and container labels submitted on 4/12/02.

Marina Chang, R. Ph.
Team Leader

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/s/

Marina Chang
4/17/02 10:49:14 AM
INTERDISCIPLINARY

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Submitted
4/10/02

NDA 21-373
CHILDREN'S ADVIL COLD SUSPENSION

CLAIM SUPPORT FOR "PEDIATRICIAN RECOMMENDED BRAND"

Reference is made to NDA 21-373 for Children's Advil Cold Suspension (ibuprofen 100mg/ pseudoephedrine HCl 15mg per 5mL). The sponsor seeks to include a graphic element on the outer carton of the product which bears the statement "Pediatrician Recommended Brand". As requested by the Agency, attached is the support for this claim.

In order to determine whether a product is recommended by physicians, a common industry source is the IMS-NDTI database. IMS surveys physicians by sampling 3,544 office based physicians covering 27 physician specialties, and then extrapolating the data to a universe of 343,655 office-based physicians. Pediatricians account for approximately 10% of office based physicians, with a universe of approximately 33,000. Real-time data is collected during 2 consecutive work days/quarter, and extrapolated for the entire year. The quarterly approach allows IMS to account for seasonal fluctuations in prescribing/recommendation practices.

Table 1 presents the top ten pediatrician-recommended analgesic products over a six year period, and any Advil recommendations that did not fall within the top ten. Pediatricians recommended Advil products by name approximately 24% of the time. These recommendations are for both specific Advil products (i.e. Jr. Strength Advil, Children's Advil) and for the general term "Advil".

These data indicate that Advil is a trusted brand with name recognition and as a result is specifically recommended by pediatricians. The data support the labeling statement "Pediatrician Recommended Brand" as a reasonable claim supported by independent data.

Table 1
Variable : Projected Drug Uses (Thousands)
Pediatrician Recommendations - Top 10 Analgesics and All Advil

	YEAR/1996	YEAR/1997	YEAR/1998	YEAR/1999	YEAR/2000	YEAR/2001	TOTAL 1996 TO 2001
MOTRIN CHILDS OTC MCC 95/09							
TYLENOL INFANT MCC 94/02							
ADVIL WHH 84/06							
ADVIL CHILDS (OTC) WHH 96/09							
MOTRIN IB MCC 89/06							
IBUPROFEN MNS 86/10							
TYLENOL JUNIOR MCC 90/06							
ADVIL JR STRENGTH (chewable) WHH 97/03							
TYLENOL CHILDRENS MCC 93/12							
EXCEDRIN MIGRAINE BMY 98/01							
ADVIL CHILDRENS WYE 89/10 (Rx)							
Total							
Total ADVIL brand recommendations							
Percent of Top 10 recommendations	22%	25%	24%	23%	27%	23%	24%

** Rx product discontinued

Source: IMS-NDTI

Submitted 11/01/02

Number of Pages Redacted 23

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Draft Labeling
(not releasable,

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-373

Whitehall-Robins Healthcare
Attention: David Smith, Ph.D.
5 Giralda Farms
Madison, NJ 07940-0871

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 Cold (ibuprofen/pseudoephedrine suspension) Suspension
100 mg/15 mg/5 mL

Review Priority Classification: Standard (S)

Date of Application: June 15, 2001

Date of Receipt: June 18, 2001

Our Reference Number: NDA 21-373

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 16, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 18, 2002 and the secondary user fee goal date will be June 18, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed 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
Attention: Division Document Room
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
Attention: Division Document Room
HFD-550
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Barbara Gould, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Mary Jane Walling
Associate Director for Regulatory Affairs,
Office of Drug Evaluation V
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research

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/s/

Mary Jane Walling
8/17/01 02:23:22 PM

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Fax

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

To: David Smith	**From:** Barbara Gould
Fax: 973 660-7187	**Fax:** 301-827-2531
Phone: 973 660-6806	**Phone:** 301-827-2019
Pages: 1 (including cover)	**Date:** 21-Aug-01
Re: NDA 21-373	

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

● Comments:

Please provide the following information or provide an explanation as to why this information was not included in the electronic submission for NDA 21-373:

> The method validation report stated in the "Table of Contents" under "Appendices D (for AQ-99-04) and E (for AQ-99-02)" in the Analytical Report for Ibuprofen (Appendix XII for AQ-99-02 and Appendix X for AQ-99-04) and Pseudoephedrine (Appendix XIII for AQ-99-02 and Appendix XI for AQ-99-04) were not included in the paper or electronic study report.

Please call if you have any questions or concerns.

BJ

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/s/

Barbara Gould
8/21/01 01:52:55 PM
CSO

010821

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Fax

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

To: David Smith	**From:** Barbara Gould
Fax: 973 660-7187	**Fax:** 301-827-2531
Phone: 973 660-6806	**Phone:** 301-827-2019
Pages: 2 (including cover)	**Date:** 03-October-01

Re: NDA 21-373 Biopharmaceutical Information Request

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

● Comments:

Please provide the following information for NDA 21-373:

Study Report AQ-00-04

1. In the Pharmacokinetic Report AQ-00-04 under the heading "Primary Pharmacokinetic Parameters" on Page 26 the applicant stated that:
"Per protocol, AUC $_{0\text{-}12}$ and CL were the primary pharmacokinetic parameters. Since there were six subjects missing blood samples at hour 12, it was decided that both AUC $_{0\text{-}9}$ and AUC $_{0\text{-}12}$ would be calculated and analyzed and AUC $_{0\text{-}9}$ would be considered the primary pharmacokinetic parameter".

Therefore according to the applicant Cmax was not considered a primary pharmacokinetic parameter and the applicant did not provide any scientific rationale for its exclusion or the analysis of another rate variable as a substitute. The applicant is reminded that at a Pre-IND meeting on November 9, 1999, they were requested by the FDA to include Cmax in the analysis for this study.

However, under the heading "Conclusion" the applicant stated that:

"In children aged 2 to <6 years, the rate and extent of absorption of pseudoephedrine hydrochloride when administered in combination with ibuprofen is acceptably similar to pseudoephedrine hydrochloride administered alone. The rate and extent of absorption of ibuprofen and pseudoephedrine hydrochloride from the combination suspension are similar across the age range of 2 to <12 years…..".

It is not clear how the applicant concluded about the rate without including Cmax as one of its primary PK parameters. Since Cmax is the primary rate variable used by the FDA and, based on the aforementioned we request that the sponsor provide information on the analysis of Cmax for within and between age group comparisons, taking the differences in dose into account for the latter.

2. In Tables 10 and 11 (Study report AQ-00-04) the applicant compared the mean AUC_{0-9} and AUC_{0-12} values between the two studies (i.e. AQ-00-02 and AQ-00-04). The applicant should please provide a table showing the individual values and the summary of descriptive statistics for these two parameters for the subjects in study # AQ-00-02.

Study Report AQ-00-02
In the Pharmacokinetic Report AQ-00-02, in Tables B.3 and B4, it appears that the CL was calculated using a dose of 110 mg instead of 220 mg for Ibuprofen and 15 mg instead of 30 mg for pseudoephedrine. Please recalculate the values for CL using the correct dose and provide the revised values.

Study Report AQ-00-02 and AQ-00-04
After recalculating the CL for AQ-00-02, please normalize CL and Volume of distribution values obtained in both AQ-00-02 and AQ-00-04 for body weight and provide the values. Then repeat the within-study and between study comparisons reported in Tables B.5, 6 and 7 in study report # AQ-00-04.

Please call if you have any questions or concerns.

BJ

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/s/

Barbara Gould
10/3/01 10:00:52 AM
CSO

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ON ORIGINAL

CONVERSATION RECORD

Date: October 18, 2001

Center Representative:	Babette Merritt, Project Manager, HFD-560
Sponsor Representative:	Dr. David Smith Director Regulatory Affairs
Sponsor Telephone Number:	973-660-6806
Name of Sponsor:	Whitehall Robins
Subject:	Request for Further Information on NDA 21-373

Conversation: (As requested by Medical Officer, Linda Hu in HFD-560, OTC)

I called Dr. Smith at Whitehall Robins and requested that they point out where pediatric ibuprofen/pseudoephedrine adverse event reports and analysis can be found in their NDA 21-373 submission for [redacted] If they cannot point out where this information is located in the submission, I asked them to provide a listing of the reports and an analysis.

I further asked him where we can find more detail about the major reports and deaths listed in the AAPCC reports (page 29/814) in the volumes for this same NDA 21-373.

He indicated that he will get check with his group and will get either a reply or the information sent to HFD-560 (OTC).

Babette Merritt, Regulatory Project Manager
October 18. 2001

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/s/

Babette Merritt
10/18/01 10:57:29 AM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 1, 2002

To: Lauren Quinn	**From:** Carmen DeBellas
Company: Whitehall-Robins Healthcare	Division of Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Fax number: RECIPIENT'S FAX NUMBER	**Fax number:** SENDER'S FAX NUMBER
Phone number: RECIPIENT'S PHONE NUMBER	**Phone number:** 301-827-2090

Subject: Information Request for Biopharm review

Total no. of pages including cover: 1

Comments:

Document to be mailed: ☐ YES ☑ NO

Attachment

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/s/

Carmen DeBellas
2/1/02 04:56:02 PM
CSO

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TELECON MINUTES

TELECON DATE: January 30, 2001 **TIME:** 3:00 p.m. **LOCATION:** Corp N426

Telecon Request Submission Date: October 26, 2000
Briefing Document Submission Date: November 09, 2000
Additional preparation documents: January 25, 2001

DRUG: Ibuprofen 100/Pseudoephedrine HCl 15mg per 5mL Suspension

SPONSOR/APPLICANT: Whitehall-Robins

TYPE of Telecon: PreNDA Type B

FDA PARTICIPANTS:	**Division of Anti-Inflammatory, Analgesics, and Ophthalmic Drug Products**
Jonca Bull, MD	Acting Division Director
Christina Fang, MD	Medical Reviewer
Joel Schiffenbauer, MD	Medical Reviewer
Abi Adebowale, Ph.D.	Biopharmaceutics Reviewer
Barbara Gould	Project Manager
	Division of Over-the-Counter Drug Products
Linda Katz, MD, MPH	Deputy Director
Linda Hu, MD	Medical Reviewer
Marina Chang, R.Ph	Team Leader Interdisciplinary Scientist
Ida Yoder	Interdisciplinary Scientist
Babette Merritt	Project Manager

INDUSTRY PARTICIPANTS:	**Whitehall-Robins**
Roger Berlin, MD	President, Global Scientific Affairs
Sharon Heddish	Vice President, Regulatory Affairs Worldwide
Joel Waksman, Ph.D.	Senior Director, Biostatistics and Data Management
Michael Chen	Director Biostatistics
Bill Thoden	Clinical Affairs
Ken Warner	Regulatory CMC
David Smith, Ph.D.	Regulatory Affairs

MEETING OBJECTIVES:
To obtain input from FDA regarding clinical program in progress that supports formulation for a NDA.

BACKGROUND INFORMATION:
Reference is made to the November 09, 1999 PreIND development meeting with the Division for the ibuprofen/pseudoephedrine suspension. The clinical program to support this formulation is in progress. If the studies are completed as planned, Whitehall plans to file a New Drug Application in May 2001.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1) **The proposed table of contents for the Application has been included in Attachment B. Is the content/format acceptable?**

   FDA Response:
   Yes.

2) **The studies undertaken as agreed upon during the FDA/Whitehall-Robins Pre-IND Meeting held on November 09, 1999 are outlined in Attachment C for the reviewer's convenience.**

3) **The Proposed Statistical Analyses Planned for the NDA has been included in Attachment D. Are there additional analyses that need to be included to meet FDA requirements?**

   FDA Response:
   The proposed statistical methods for the pharmacokinetic studies in protocols AQ-99-02 and AQ-99-04 and the combination of both protocols included in attachment D are acceptable.

4) **We provide data sets containing information collected in CRFs, patient plasma concentration data, and derived PK data. Data will be generated as export files. Is this adequate?**

   FDA Response:
   Yes.

5) **The proposed safety package for the Application has been included in Attachment E. Whitehall-Robins feels that this package is sufficient for the NDA. Please provide feedback on the adequacy of the safety package as outlined. Whitehall-Robins also seeks input from FDA if reduced safety package would appropriate for this application.**

   FDA Response:
   In safety data analysis the following information should include:

   1. Drug exposure in terms of duration of exposure, correlation between the drug exposure and adverse events, age/gender difference in adverse event reporting for safety data obtained from clinical studies;
   2. Serious events (reported from any of the data sources) associated with the use of the combination product as well the concomitant use of ibuprofen and pseudoephedrine products to be listed for the individuals with regard to age, drug exposure, outcome of events, and assessment of causal relationship in a chart/tabular format;

3. Adverse events from concomitant use of products containing ibuprofen and pseudoephedrine, in addition to the combination products, from all data sources including SRS, AERS, poison control, and abuse data;
4. Tabulated summary of safety data from literature review;
5. Safety data on the use of combination product and concomitant use of the ibuprofen and pseudoephedrine products to cover all ages and age groups (age <2, 2 to <12, ≥12); safety data on individual ingredients to cover pediatric groups (age <2 and 2 to <12);
6. Update of the safety data to the time of submission of the NDA;
7. Marketing History of the ibuprofen/pseudoephedrine combination in terms of
   - Where the combination has been marketed, registered and/or licensed
   - What the current marketing status is: Rx or OTC
   - Dosage strength/concentration, dosing schedules, and use for what age range
   - Whether the drug has ever been withdrawn from the market and, if so, for what reason

Note: If the sponsor wants pediatric exclusivity consideration the Written Request needs to be followed very carefully.

Whitehall Question:
We are having problems with enrollment for pharmacokinetics study AQ-99-00-04 and based on written communication received December 12, 2000 from BioPharm with regard to the option to amend the Pediatric Written Request, how long would it take to get a response to the amendment?

FDA Response:
You could expect a response to the amendment within 45 days of submission.

6) The Chemistry, Manufacturing and Controls package will support the 100-mg ibuprofen concentration of the formulation as had been agreed upon. The CMC package outlined is outlined is included in Attachment F.

FDA Response:

A. Since the commercial formulation will provide 100-mg ibuprofen, USP per 5-mL drug product, it is more appropriate that the formulations that contain 110-mg ibuprofen, USP per 5 mL be included in the section for "Investigational Formulation".

B. [redacted], expiration date will not be granted with the submission of 9-month stability data in the NDA submission.

C. To support an expiration-dating period, stability data on pilot batches should be included in the NDA submission.

7) **Whitehall-Robins is planning to submit a fully electronic NDA that is compliant with CDER guidelines for electronic NDA submission. The overview is included in Attachment G. Does the Agency agree with the Electronic Submission Proposal? Does the FDA agree with the contents of the paper review copy? How many review copies FDA require?**

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

Please submit 10 paper copies. Please also submit a paper review copy of the clinical section for OTC. Please provide reviewers aid that will include a table containing clinical data in Word 97 format.

8) **Draft labeling for the product will be submitted with the NDA. Please provide feedback on the total number of copies of each component of the draft labeling to be included in the NDA.**

FDA Response:
1. Please submit a minimum of four copies of each component in hard copy.
2. Two text file in "Word 97" for each component (HFD-550 and HFD-560 will each have their own copy).
3. Please provide specifications for font sizes for title, headings, subheadings, condensed text and other graphic features. for specification requirements.

ADDITIONAL FDA COMMENTS:

Financial Disclosure:
We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective, or that makes a significant contribution to demonstration of safety. Please refer to "Financial Disclosure by Clinical Investigators" Final Rule February 2, 1998.

ACTION ITEMS:

1. Telecon will be scheduled to discuss CMC and Pharmacokinetic issues.
2. The project manager will convey minutes within 30 days.

Barbara Gould March 19, 2001
Barbara Gould Date
Project Manager

Concurrence Chair: *Jonca C. Bull, MD March 19, 2001*
Jonca C. Bull, MD Date
Acting Division Director

Initialed by: CFang/*02-09-01 w/changes*
AAdebowale/*02-09-01 w/changes*
LHu/*02-09-01 w/changes*
IYoder/*02-09-01*
LKatz/ *02-14-01 w/changes*
JBull/*03-19-01*

MEETING MINUTES
Faxed to sponsor and DFS 03-21-01

/s/

Jonca Bull
4/3/01 09:09:11 AM

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ON ORIGINAL

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA: **30-May-2002** Application Written Request was made to ~~_____~~
Timeframe Noted in Written Request for Submission of Studies **01-Jan-02**.
NDA 21-373 Supplement # **N/A** Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
Sponsor: **Whitehall –Robins Healthcare**
Generic Name: **Ibuprofen/pseudoephedrine HCl** Trade Name: **Children's Advil Cold Suspension**
Strength: **100 mg/15 mg/5 mL** Dosage Form/Route: **Oral**
Date of Submission of Reports of Studies: **19-June-01**.
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) **18-Sept-01**.

Was a formal Written Request made for the pediatric studies submitted?	Y ✓	N ___
Were the studies submitted after the Written Request?	Y ✓	N ___
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y ✓	N ___
Was the timeframe noted in the Written Request for submission of studies met?	Y ✓	N ___
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y ✓	N ___
Did the studies fairly respond to the Written Request?	Y ✓	N ___

FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-002.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity **X Granted** **___ Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
Exclusivity would attach only to 3-year Hatch-Waxman exclusivity once application is approved		

SIGNED _____ (See appended electronic signature page) 9/19/01

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/s/

Terrie Crescenzi
9/21/01 03:05:51 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 30 2000

RECEIVED

JUL 31 2001

CDR/CDER

Whitehall-Robins Healthcare
Attention: Joanne Robinett
Director, Regulatory Affairs
Five Giralda Farms
Madison, New Jersey 07940-5500

Dear Ms. Robinett:

Reference is made to your Proposed Pediatric Study Request submitted on December 22, 1999, for ibuprofen/pseudoephedrine HCl suspension.

To obtain needed pediatric information for ibuprofen/pseudoephedrine HCl suspension for the treatment of symptoms associated with common cold and flu, including nasal congestion, headaches, body aches and pains, and fever, the Food and Drug Administration (FDA) is hereby issuing to you an official Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act. FDA requests that you submit information from the following three studies:

Type of Studies:

Study 1: A single-dose pharmacokinetic study of ibuprofen/pseudoephedrine HCl suspension in healthy children ages 6 through 11 years.

Study 2: A single-dose confirmatory pharmacokinetic study in children ages 2 through 5 years with symptoms of an acute upper respiratory infection.

Study 3: A multiple-dose safety study of ibuprofen/pseudoephedrine HCl suspension in at least 75 children ages 2 through 11 years with symptoms of an acute respiratory infection to be dosed as recommended in the proposed labeling.

Indication/Objective:

Study 1: The primary objectives of the study are to evaluate the single-dose pharmacokinetic parameters of the combination product of ibuprofen/ pseudoephedrine suspension and to assess the potential for a drug-drug pharmacokinetic interaction by comparing the results with those of the components administered individually.

Study 2: The primary objectives of the study are to evaluate the single-dose pharmacokinetic parameters of the combination product of ibuprofen/ pseudoephedrine suspension and to assess the potential for a drug-drug

pharmacokinetic interaction by comparing the results with those of pseudoephedrine administered alone.

Study 3: The primary objective of the study are to evaluate the safety of repeated administration of ibuprofen/pseudoephedrine HCl suspension in pediatric patients of the target population.

Study Design:

Study 1: This study should be a single-dose, randomized, three-way crossover (ibuprofen/pseudoephedrine combination, pseudoephedrine, ibuprofen) pharmacokinetic study.

Study 2: This study should be a single-dose, randomized, parallel (ibuprofen/pseudoephedrine combination vs. pseudoephedrine alone) pharmacokinetic study.

Study 3: This study should be a multiple-dose safety study of the ibuprofen/pseudoephedrine combination.

Age Groups:

Study 1: The study should be conducted in pediatric subjects (at least 24 completers) spanning the age range of 6 through 11 years, at least 50% of whom should be approximately evenly distributed throughout the age range of 6 through 8 years.

Study 2: The study should be conducted in pediatric patients (at least 40 completers; at least 20 per arm) spanning the age range of 2 through 5 years, at least 50% of whom should be approximately evenly distributed throughout the age range of 2 through 3 years.

Study 3: The study should be conducted in pediatric patients (at least 75 completers) spanning the age range of 2 through 11 years, with approximately even distribution throughout the age range of 2 through 11 years.

Drug Information:

Dosage Form: Suspension

Route of Administration: Oral

Drug Specific Safety Concerns:

Study 1, 2, & 3: Clinical safety for each study should include monitoring for development or exacerbation of asthma, anaphylactoid reactions, central nervous system effects, and hemodynamic effects.

Statistical Analysis:

Studies 1& 2: In order to provide a sufficiently accurate estimate of any dosing adjustments that may be needed in pediatric subjects, the planned pharmacokinetic evaluation should be powered and structured to detect a 30% change in drug clearance and other relevant pharmacokinetic parameters compared to values for the administration of the individual ingredients to children. In addition to the primary analysis, a covariance analysis should be performed considering gender, age and body weight.

Study 3: Statistical analyses should include baseline demographics (age, gender, weight, race); incidence rates of adverse events and premature withdrawals; and changes from baseline in vital signs. All analyses should be summarized and safety data should be tabulated, including serious and other adverse reactions, deaths, withdrawals and dropouts.

Labeling:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of Reports to Be Submitted:

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation must be submitted.

Timeframe:

These reports must be submitted by January 1, 2002. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not been extended previously or has not expired at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please note that you may seek a written agreement with FDA, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act)*. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to your approved NDA with the proposed labeling changes that you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact Sandra Cook, Project Manager, at (301) 827-2090.

Sincerely yours,

/S/

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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