CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-374

ADMINISTRATIVE DOCUMENTS

K1.2

N21374

ACTION PACKAGE

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6/26/02
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NDA 21-374

ADVIL COLD & SINUS LIQUEGEL

BY WHITEHALL ROBINS

Receipt Date: July 30, 2001
Filing Date:
Fileability Meeting Date: September 5, 2001
User Fee Goal Date: May 30, 2002

Project Manager: Babette Merritt, OTC (HFD-560),
Team1

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 Suspension and 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.

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

/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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EXCLUSIVITY SUMMARY for NDA # 21-374 SUPPL # _____

Trade Name Advil Cold & Sinus Liquigel
Generic Name ibuprofen 200mg/pseudoephedrine HCl 30mg
Applicant Name Wyeth Consumer Healthcare HFD- 560
Approval Date May XX, 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 /___/ NO /_X_/

      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.

      Already established efficacy

      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 /___/ 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 # _____ _____

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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 #	21-128	Children's Motrin Cold
NDA #	19-771	Advil Cold & Sinus
NDA #	19-899	Sine-aid IB

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 /_X_/

Approval is based on a biostudy comparing the liquigel formulation to the tablet (NDA 19-771) previously approved. There was also a biostudy on the liquigel under fed and fasted conditions.

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 signature page)
Signature of Preparer — Date

Title:_____

Signature of Office of Division Director — Date

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

ITEM 14: PATENT CERTIFICATION

The undersigned declares that U.S. Patent Nos. 5,071,643 and 5,360,615 cover the formulation, composition and/or method of use of ADVIL® COLD AND SINUS LIQUIGELS®. This product is the subject of this application for which approval is being sought.

WHITEHALL-ROBINS HEALTHCARE

David S Smith

David S. Smith, PhD
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ITEM 13: PATENT INFORMATION

Pursuant to 21 CFR 314.53, Whitehall-Robins Healthcare, a division of American Home Products Corporation, herewith submits patent information for ADVIL® COLD AND SINUS LIQUI-GELS® (ibuprofen 200mg and pseudoephedrine HCL 30mg).

The undersigned declares that U.S. Patent Nos. 5,071,643 and 5,360,615 cover the formulation of this ibuprofen/pseudoepherine-containing dosage form. These U.S. patents are assigned to R. P. Scherer Corporation and are licensed to American Home Products Corporation of which the Applicant is a division. Whitehall-Robins Healthcare is hereby including the patent information (Exhibit A) for this NDA.

WHITEHALL-ROBINS HEALTHCARE

David S Smith

David S. Smith PhD

Director, Regulatory Affairs

APPEARS THIS WAY
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EXHIBIT A: Patent/Exclusivity Information

1)	Active Ingredients	Ibuprofen / Pseudoephedrine HCl
2)	Strength	200mg Ibuprofen 30mg pseudoephedrine HCL
3)	Tradename	ADVIL® COLD AND SINUS LIQUIGELS®
4)	Dosage Form, Route of Administration	Liqui-Gel® Gelatin Capsule, Oral
5)	Applicant Firm Name	Whitehall-Robins Healthcare, Division of American Home Products Corporation
6)	NDA Number	21,374
7)	Approval Date	Pending
8)	Exclusivity – Date first ANDA could be approved and length of exclusivity period:	Pursuant to clause (iii) of Section 505 (j)(4)(D) of clause (iii) of Section 505 (c)(3)(D) of the Federal Food, Drug and Cosmetic Act, as amended, no ANDA may be approved and made effective prior to three (3) years after the date of approval of this NDA. This NDA contains "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application" included in the data submitted to support indications for the drug in the temporary relief of cold, sinus and flu symptoms.

9. Applicable Patent Information:

U.S. Patent No. 5,071,643

Expires: December 10, 2008

Type: Drug Product

Owner: R. P. Scherer Corporation

U.S. Patent No. 5,360,615

Expires: December 10, 2008

Type: Drug Product

Owner: R. P. Scherer Corporation

APPEARS THIS WAY
ON ORIGINAL

ITEM 14: PATENT CERTIFICATION

The undersigned declares that the US Patent Nos. 5,071,643 and 5,360,615 cover the formulation, composition and/or method of use of ADVIL ® COLD AND SINUS LIQUIGELS®. This product is the subject of this application for which approval is being sought.

Furthermore, 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

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ON ORIGINAL

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

NDA # 21-374

Addendum Date : 4/26/02, 5/13/02
Review Date : 5/16/02

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

Applicant's Representative: David S. Smith
Director Regulatory Affairs
Development & Regulatory Affairs

Drug: Advil Cold & Sinus Liquigels
Ibuprofen 200 mg /Pseudoephedrine HCl 30 mg

Pharmacological Category: Pain Reliever/Fever Reducer/Nasal Decongestant

Submitted:

A. 16-count carton *draft* labeling

B. 32-count carton *draft* labeling

Reviewer's Comment:

The sponsor has complied with the Agency's labeling recommendations, dated 4/16/02 and via telephone communications on 4/17/02 and 4/30/02. The mock-ups for the sponsor's 16- and 32-count carton labels submitted on 5/13/02 are satisfactory.

Recommendation: The application is approvable based on the 16- and 32-count carton labels submitted on 5/13/02 and the blister pack label submitted on 7/24/01.

Cazemiro R. Martin
IDS: Reg. Review Chemist

Debbie Lumpkins
Team Leader

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

/s/

Cazemiro Martin
5/16/02 09:39:52 AM
INTERDISCIPLINARY

Debbie Lumpkins
5/16/02 09:52:35 AM
INTERDISCIPLINARY

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WITHHOLD 2 PAGE (S)

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-374 Supplement Type (e.g. SE5): _____ Supplement Number: _____

mp Date: July 30, 2001 Action Date: May 30, 2002

HFD -560 Trade and generic names/dosage form: Advil Cold & Sinus Liquigels

Applicant: Wyeth Consumer Healthcare Therapeutic Class: 3S

Indication(s) previously approved: none

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

Number of indications for this application(s): 1

Indication #1: for temporary relief of symptoms associated with the common cold, sinusits, or flu, including nasal congestion, headache, fever, body aches and pains

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

☑ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

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

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

ion C: Deferred Studies

Age/weight range being deferred:

Min____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Reason(s) for deferral:

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

Other:_____

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies:

Min____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

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

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

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

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

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

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

tion C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337