CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-373

CHEMISTRY REVIEW(S)

NDA 21-373

Children's Advil Cold suspension

Whitehall-Robins

Bart Ho
HFD-550

Table of Contents

Table of Contents 2
Chemistry Review Data Sheet 4
The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Substance(s) and Drug Product(s) 8

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative 10

A. Reviewer's Signature N/A 10

B. Endorsement Block N/A 10

C. CC Block N/A 10

A. DRUG SUBSTANCE 11

B. DRUG PRODUCT 11

1. Components/Composition 11

2. Acceptance Criteria & Methods for Drug Product Ingredients 12

3. Manufacturer 12

4. Methods of Manufacturing and Packaging 12

a. Production Operations 13
b. In-Process Controls & Tests 14
c. Reprocessing Operations: 14

5. Regulatory Acceptance Criteria and Methods for Drug Product 14

a. Sampling Procedures: Sampling procedures are provided. 14
b. Regulatory Acceptance Criteria and Methods 14

6. Container/Closure System 24

7. Microbiology: 28

8. Drug Product Stability 28

III. INVESTIGATIONAL FORMULATIONS 40

IV. ENVIRONMENTAL ASSESSMENT 40

V. METHODS VALIDATION 40

VI. LABELING 40

VII. ESTABLISHMENT INSPECTION 41

Chemistry Review Data Sheet

1. NDA 21-373

2. REVIEW #: 1

3. REVIEW DATE: 4/5/02

4. REVIEWER: Bart Ho

5. PREVIOUS DOCUMENTS:

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	6-15-01
Amendment 1	8-3-01
Amendment 2	1-16-02
Amendment 3	2-14-02
Amendment 4	3-5-02
Amendment 5	4/1/02
Amendment 6	4/2/02
Amendment 7	4/4/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Whitehall-Robins
Address:	Five Giralda Farms, Madison, NJ 07940-0871
Representative:	Ken Warner Director, Regulatory Affairs
Telephone:	973-660-6896

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Children's Advil Cold suspension
   b) Non-Proprietary Name (USAN): Ibuprofen/Pseudoephedrine HCl
   c) Code Name/# (ONDC only):N/A
   d) Chem. Type/Submission Priority (ONDC only):

   - Chem. Type: 3
   - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

   N/A

10. PHARMACOL. CATEGORY:

    NSAID

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: Ibuprofen, 100 mg/Pseudoephedrine HCl, 15 mg per 5 mL

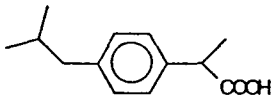
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed

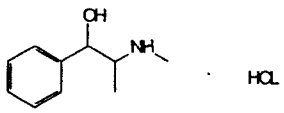
    ___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(±)-2-(p-Isobutylhydratropic acid

Molecular Formula: $C_{13}H_{18}O_2$
M. W. 206.29



Benzenemethanol, α-[1-(methylamino)ethyl]-, [S-(R,R)]-, hydrochloride

$C_{10}H_{15}NO.HCl$
201.70

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF#	Type	Holder	Item/Component	Code	Status	Date Review	Comment
	III			4*			
	III			3	Adequate	3/6/01	
	III		P)	3	Adequate	11/20/02	
	III		3	3	Adequate	4/3/01	
	IV			3	Adequate	10/13/93	
	IV			3	Adequate	4/3/01	
	III			3	Adequate	6/30/95	
	IV						
	III			3	Adequate	8/2/99	
	I			2			
1	IV			7			See note 1
	IV			7			See note 1
	III			4			
	II			3	Adequate	2/14/01	
	II			3	Adequate	9/12/01	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Reviewer's Note #1:

The DMF does not contain any deficiency letter for the materials referenced in the NDA. Information provided in the DMF is sufficient. The color is FDA certified. A detailed review was not performed.

* Firm has provided sufficient safety information in amendment dated 2/14/02.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	

18. STATUS: None

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	2/25/02	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Sent to FDA lab for validation		
OPDRA	N/A		
EA	Categorical Exclusion		
Microbiology	N/A		

The Chemistry Review for NDA 21-373

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval based on the CMC information submitted

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Substance(s) and Drug Product(s)

1) Drug Substances

Ibuprofen:

The ibuprofen drug substance is manufactured by —— —— .. Manufacture and control of the drug substance were referenced to the drug master file

Pseudoephedrine HCl:

The pseudoephedrine HCl drug substance is manufactured by —— —— . Manufacture and control of the drug substance were referenced to the drug master file # ——

2) Drug Product

Children's Advil Cold Suspension is an aqueous suspension and contains ibuprofen, 100 mg/5 mL and pseudoephedrine HCl 15 mg/5 mL packaged in 4 oz polypropylene and 8 oz high density polyethylene bottles. In the manufacturing process, ibuprofen is introduced in a mixer as a solid and pseudoephedrine as an aqueous solution. To assure uniformity of the final drug product, proper mixing of all the ingredients is critical. In addition, maintaining appropriate viscosity of the suspension is important to assure uniformity of the drug product. Due to rapid dissolution of the drug product, particle size of the ibuprofen drug substance is not considered as an important factor.

FDA recommended, in a pre-IND meeting, that the firm should conduct clinical studies using a drug product formulation that contained 110 mg of ibuprofen per 5 mL dose. Initial clinical studies, therefore, were performed on three batches that contained 110 mg/5 mL ibuprofen. FDA subsequently requested the formulation be changed to 100 mg of ibuprofen per 5 mL dose. Concentration of pseudoephedrine HCl in the two formulations remained the same at 15 mg/5 mL. Batches for commercial distribution will contain ibuprofen 100 mg/5 mL and pseudoephedrine HCl 15 mg/5 mL.

B. Description of How the Drug Product is Intended to be Used

The drug product, **Children's Advil Cold Suspension,** is an aqueous suspension, and is orally administered for temporary relief of the cold, sinus and flu symptoms and will be marketed in 4 oz polypropylene —— high density polyethylene bottles. Firm's request for 24 months expiration date, based on the stability data submitted, is acceptable. The drug product is recommended to be stored at room temperature, 20-25°C (68-77°F).

C. Basis for Approvability or Not-Approval Recommendation

The quality control of the drug substance ibuprofen was referenced to ——
Pseudoephedrine HCl was referenced to —— They have been recently reviewed and were found adequate. Tests and acceptance criteria of these two drug substances meet the requirements of USP.

As discussed in the previous section, the drug product was initially formulated to contain 110 mg of ibuprofen per 5 mL. **Children's Advil Cold Suspension** will be formulated to contained 100 mg of ibuprofen per 5 mL for commercial distribution. Concentration of pseudoephedrine HCl in the two formulations remained the same at 15 mg/5 mL. The differences in the amount of ibuprofen contained in the two formulations, 110 mg/5 mL to 100 mg/5 mL are small and therefore, are not deemed great enough, from a chemistry standpoint of view, to cause concern that comparability studies are needed.

The sponsor has demonstrated stability of the drug product based on the submission of long term stability data, 18 months on three batches, 21 months on one clinical batch on the formulation containing 110 mg/5 mL ibuprofen and pseudoephedrine HCl 15 mg/5 mL, and 12 months on one batch that contained 100 mg/5 mL ibuprofen and pseudoephedrine HCl 15 mg/5 mL.

Stability data indicated that the drug product is stable for the period studied when stored in the proposed container/closure systems. Little or no degradation was found. Potencies vary; however, there is no evidence that a trend in decreasing in potency existed for the period studied.

Stability studies indicated that separations or aggregations of the suspended drug product occurred during storage. It was demonstrated that incomplete mixing (shaking) of the sample caused the low initial result. Firm's container label did contain a warning statement "shake well" in the "direction" section. The reviewer suggests that these two words should be displayed more prominently.

Appropriate release and stability tests (and acceptance criteria) have been established to assure the drug product quality. They were considered to be adequate after the firm agreed to the tightened acceptance criteria for the known impurities and dissolution criterion based on current manufacturing experience and stability data. Firm was also requested to add acceptance criteria for total degradants and unspecified degradants, individual and total, in the drug product.

It is recommended that NDA-373 be approved based on the CMC information submitted.

III. Administrative

A. Reviewer's Signature N/A

B. Endorsement Block N/A

C. CC Block N/A

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

33 pages

(pages 11-43)

12-MAR-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21373/000** Priority: Org Code: **550**
Stamp: **18-JUN-2001** Regulatory Due: **18-APR-2002** Action Goal: District Goal: **17-FEB-2002**
Brand Name: **CHILDREN'S ADVIL COLD SUSPENSION(IBUPROFEN)**
Applicant: **WHITEHALL ROBINS**
1001 SOUTH GRAND ST
HAMMONTON, NJ 08037 Established Name:
Generic Name: **IBUPROFEN/PSEUDOEPHEDRINE**
Dosage Form: **SUS (SUSPENSION)**
Strength: **100 MG/15 MG PER 5 ML**

FDA Contacts:	**B. GOULD**	**(HFD-550)**	**301-827-2090,**	**Project Manager**
	B. HO	**(HFD-550)**	**301-827-2050,**	**Review Chemist**
	J. SMITH	**(HFD-550)**	**301-827-2529,**	**Team Leader**

Overall Recommendation:
ACCEPTABLE on 25-FEB-2002 by J. D. AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 20-FEB-2002 by J. D. AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted] DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **20-FEB-2002**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted] DMF No:
AN AADA No:

Profile: **CSN** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **30-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **1110584** DMF No:
WYETH AYERST LABORATORIES AADA No:
1407 CUMMINGS DR
RICHMOND, VA 23220

Profile: **CTL** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE RELEASE TESTER**
Last Milestone: **OC RECOMMENDATION**

Chemistry Assessment Section

Milestone Date: **26-JUL-2001**
Decision: **ACCEPTABLE**

Reason: **DISTRICT RECOMMENDATION**

Establishment: **1120199** DMF No:
WYETH AYERST LABORATORIES AADA No:
2248-2258 DARBYTOWN RD
RICHMOND, VA 23231

Profile: **LIQ** OAI Status: **NONE**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY REVIEW

Chemistry Assessment Section

METHODS VALIDATION REQUEST AND REPORTING RECORD	NDA No. 21-373

1. SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION
Drug product	Enough to perform all the tests.	

2. Contents of Attached Methods Validation Package ==========>		
	Statement of Composition of Finished Dosage Form(s) Specifications/Methods for New Drug Substance(s) Specifications/Methods for Finished Dosage Form(s) Supporting Data for Accuracy, Specificity, etc. Applicant's Test Results on NDS and Dosage Forms Other:	All are provided

3. REQUESTED DETERMINATIONS (Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.)

Dosage Form

Tests **Specification**

4. SUMMARY OF RESULTS (Report individual and average ASSAY results.)

Signature of Analyst:	Date:

DATE	FIELD LABORATORY COPY ROUTING	DATE	☐ DDA or ☐ DRT COPY ROUTING
	Forwarded to Reviewing Chemist		Forwarded to Reviewing Chemist
	Received by Reviewing Chemist		Received by Reviewing Chemist

MR/Method Validation Report (Attach additional pages, if needed.)

Form 2871a (8/96)

Originator: Bart Ho, HFD-550, 301-827-2502

CHEMISTRY REVIEW

Chemistry Assessment Section

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

FROM: Bart Ho, HFD-550 Tel. No. (301)-827-2502
(Reviewing Chemist)

Through: John Smith, HFD-550 Tel. No. (301)-827-2296
(Chemistry Team Leader)

SUBJECT: Methods Validation for NDA No. 21-373

Product: Children's Advil Cold Suspension

Applicant: Whitehall-Robins

Address: Five Giralda Farms, Madison, NJ 07940-0871

(Date Below)
TO: ☐ San Juan District Office, PR, HFR – SE 560 2/11/02
(Pre-Approval Laboratory)

Date NDA/ANDA Received by CDER: / /
Type: Chemical/Therapeutic
Special Handling Required: per MSDS (attached, page)

DEA Class PAC: ☐ 52832 (ANDA's) ☐ 46832 (NDA's)

This is to confirm the suitability of the proposed manufacturing controls as described in the subject application. The samples identified in the attached Form 2871a (Methods Validation Request and Reporting Record) will be provided to you by the applicant. Please perform the tests indicated in item 3 of 2871a as described in the accompanying MV package, and summarize your laboratory results in item 4. Also, please include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes. All information relative to this application is to be held confidential as required by 21 CFR 314.430.

Because of statutory time limits for processing applications, we request your report to be submitted promptly upon completion, but not later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. Please promptly advise the reviewing chemist of the date the validation process begins. If the requested completion date cannot be met, please promptly notify the reviewing chemist.

Upon completion of the requested validation/verification, please assemble the necessary documentation (i.e., the original signed 2871a with original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying memoranda). At the bottom of the report signed by the laboratory director, place the filing code: **"MR/Method Validation Report."** Send by overnight courier to the above reviewing chemist.

ENCLOSURE: Form 2871a and NDA/ANDA Methods Validation Package.

Originator: Bart Ho, Review Chemist, HFD-550

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

/s/

Bartholomew Ho
4/8/02 12:06:41 PM
CHEMIST

John Smith
4/8/02 01:32:10 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL