

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-402/SCM-001/S-002/S-003/S-004/S-005

CHEMISTRY REVIEW(S)

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-402 **REVIEW #:** 1 **DATE REVIEWED:** 7-APR-99

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
SCS-004	20-NOV-1998	27-NOV-1998	12-FEB-1999

NAME & ADDRESS OF APPLICANT: WHITEHALL-ROBINS HEALTHCARE
5 Giralda Farms
Madison, NJ 07940

DRUG PRODUCT NAME

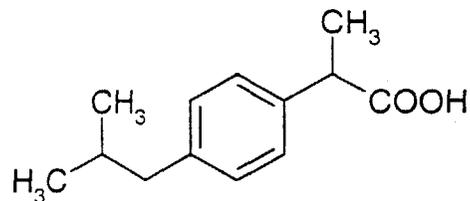
<u>Proprietary:</u>	Advil® Liquigel®
<u>Established:</u>	Ibuprofen, USP
<u>Code Name/#:</u>	None
<u>Chem.Type/Ther.Class:</u>	2-(4-isobutylphenyl) Propionic Acid

PHARMACOL. CATEGORY/INDICATION:

<u>DOSAGE FORM:</u>	Liquigel (Liq core/soft gelatin shell)
<u>STRENGTHS:</u>	200 mg
<u>ROUTE OF ADMINISTRATION:</u>	Oral
<u>Rx/OTC:</u>	___ Rx <u>X</u> OTC

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

Molecular Formula: C₁₃H₁₈O₂ Molecular Weight: 206.29



SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS: None

REMARKS/COMMENTS:

This "Special Supplement-Changes Being Effected" provides for the addition of a new specification (i.e. in-process pH specification) for the liquid fill material prior to encapsulation as recommended by the FDA. The supplement is filed to fulfill the firm's post-approval commitment made in the NDA amendment dated February 14, 1995, response #2, page 7.

Based on the historical data for [] batches of Advil Liquigels, an in-process pH specification of [] is acceptable.

CONCLUSIONS & RECOMMENDATIONS:

The proposed in-process pH specification of [] is acceptable.

The supplemental application is recommended for APPROVAL for manufacturing and controls section under 505 of the Act.

IS/

/4/9/99

Mamta Gautam-Basak, Ph.D.
Review Chemist, HFD-540

cc:

- Org. NDA 20-402 SCS004
- HFD-560/Division File
- HFD-540/Chem/MGautambasak
- HFD-560/PM
- HFD-550/TL/HBPATEL
- HFD-830/Chi-W.Chen

R/D Init by: TEAMLEADER

APPEAR THIS WAY
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This portion of the document contains information that will not be included in the redacted portion of the document for the public to obtain.

FEB 2 1999

CHEMIST REVIEW
OF SUPPLEMENT

1. ORGANIZATION HFD-560
2. NDA NUMBER: 20-402
3. SUPPLEMENT NUMBERS/DATES: SCP-003
Letter date: 9/30/98
Stamp date: 10/5/98
Due date: 2/5/98 (4 mo. PDUFA)
4. AMENDMENTS/REPORTS/DATES:
Letter date: 1/26/99
Stamp date: FAX
5. RECEIVED BY CHEMIST: 10/29/98

6. APPLICANT NAME AND ADDRESS: Whitehall-Robins Healthcare
5 Giralda farms
Madison, NJ 07940

7. NAME OF DRUG: Advil³ Liquigel[®]

8. NONPROPRIETARY NAME: ibuprofen

9. CHEMICAL NAME/STRUCTURE: see USP

10. DOSAGE FORM(S): liquid filled soft gelatin capsule

11. POTENCY: 200 mg

12. PHARMACOLOGICAL CATEGORY:

13. HOW DISPENSED: OTC

14. RECORDS & REPORTS CURRENT:

15. RELATED IND/NDA/DMF: see attached list of DMFs referenced.

16. SUPPLEMENT PROVIDES FOR: changes in the packaging components for the bottles and blisters and the addition of pouch packaging.

17. COMMENTS

This supplement proposes that the packaging components for the bottles and blisters be changed to those currently approved in NDA 18-989 for Advil 200 mg (swallow) tablets. It also proposes to add a pouch packaging configuration.

18. CONCLUSIONS AND RECOMMENDATIONS: APPROVE contingent on results of labeling review.

19. REVIEWER NAME

SIGNATURE

DATE COMPLETED

Charlotte Yaciw

/S/
/S/

2/1/1999

Concurrence: Hasmukh Patel

2/2/99

cc: Original: 20-402
 HFD-560/Division File
 HFD-560/PM/KRothschild
 HFD-550/Chem/CYaciw
 HFD-830/CWChen

DMFs referenced

DMF #	Holder	Subject	LOA	Status
			7/24/95	Adequate ¹
			4/10/92	Adequate ¹
			7/31/95	Adequate ¹
			8/1/95	Adequate ¹
			4/3/97	Adequate ²
			8/17/93	Adequate ¹
			7/31/95	Adequate ¹
			3/7/97	Adequate ¹
			2/18/97	Adequate ¹
			2/10/97	Adequate ¹
			4/7/98	na ⁴

¹Found adequate for [redacted] which was approved 12/98.

²Found adequate 4/17/96; no additional data has been submitted; the annual report dated 2/26/98 states that the DMF is current.

³[redacted] does not maintain a DMF for the plastic snap caps but references for the resin and colorant were provided.

⁴DMF not reviewed – adequate information was provided with the LOA.

APPROVED BY
 ON ORIGINAL

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SEP 30 1997

Chemistry Review #1	1. Division HFD-550	2. NDA & Suppl. Number 20-402/S-001
3. Name and Address of Applicant Whitehall-Robins Healthcare 5 Giralda Farms Madison, NJ 07940-0871		4. Supplement Number Date S-001 11/11/96
5. Name of Drug Provel [®]	6. Nonproprietary Name: Ibuprofen	
7. Supplement Provides for: The use of Wyeth-Ayerst, 64 Maple Street, Rouses Point, NY 12979 to packaging and testing of the drug product.		8. Amendment(s) 5 2 97
9. Pharmacological Category Analgesic	10. How Dispensed, OTC	11. Related Documents None
12. Dosage Form, Liquid Gels (liquid core, soft gelatin shell)	13. Potency(ies), 200 mg	
14. Chemical Name and Structure see USAN		
15. Comments See review below.		
16. Conclusions and Recommendations: An approvable letter has been sent to the firm previously. Recommend Approve this time.		
17. Name of the review chemist Bart Ho, Chemist	Signature 	Date 8-14-97
Team Leader Hasmukh Patel	Signature 	Date 9-30-97

cc:

NDA 20-402
HFD-550/Division File
HFD-550/B. Ho
HFD-550/CSO

HFD 550/4211-1-17-97

Purpose of the Submission: To respond FDA comments sent to the firm in the approvable letter.

FDA Comments (provided in italic):

Question 1: Please provide information on the Quality Control upon receipt of packaging material and bulk tablets. Is an identity test performed if a certificate of analysis for bulk tablets is received? We recommend that you conduct full NDA testing if COAs of the drug product is not received.

Question 2: We note that subsequent to commercial distribution of packaged product from the Rouses Point facility, one additional batch will be entered into the packaged product stability program and will be tested at yearly intervals. Please note that stability test performed at reduced level than currently approved requires the submission of a pre-approval supplement before the change can be made.

Question 3: Your commitment to place first three production batches in each of the two different packaging configuration, HDPE and blisters is insufficient. If there are more than one container/closure systems commercially available, Stability study for a given strength should include drug products stored in the smallest and the largest container/closure systems.

Question 4: Please commit to withdraw the drug product from the market any lots found to fall outside the approved specifications or immediately discuss with the reviewing division if the deviation is a single occurrence that does not affect the safety and efficacy of the drug product.

Firm's Response to FDA comment 1:

Acceptance tests and specifications were provided in NDA submission dated 9/24/93 (pages 03-00190-0300216). A minimum of one identification test will be performed for each receipt of packaging components.

Review Chemist's Comment: Response is adequate.

Firm's Response to FDA comment 2:

A description of stability tests conducted at the initial and post approval are provided.

Review Chemist's Comment: Response is adequate.

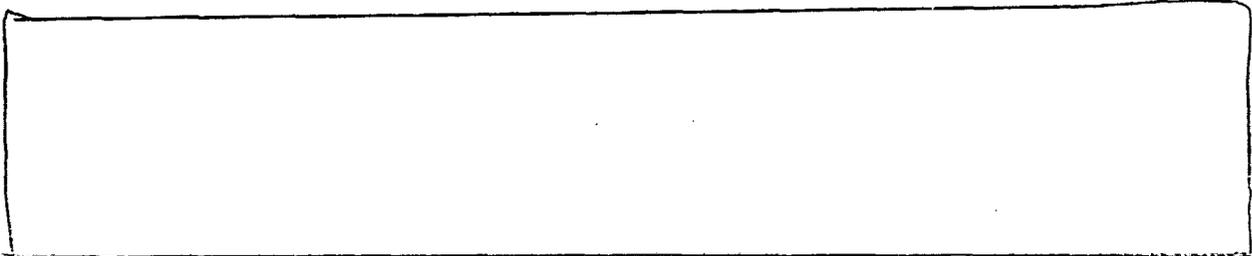
Firm's Response to FDA comment 3:

See the response above.

Review Chemist's Comment: Response is adequate.

Firm's Response to FDA comment 4:

Stability commitment is provided.



Review Chemist's Comment: Response is adequate but with comment.

[Redacted] Batches on stability should be randomly selected from the production packaging equipment of a production run to assure that a batch on stability statistically represents a commercially distributed batch. This is an approved NDA. We will not comment at this time.

Conclusions and Recommendations:

Response is adequate. The submission is complete. Recommend Approve

APPEARS THIS WAY
ON ORIGINAL