

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-393 & 21-394**

**CHEMISTRY REVIEW(S)**

**NDA 21-393**

**Advil PM Liquid-Gels**

**Wyeth Consumer Healthcare**

**Bart Ho  
HFD-550  
HFD-560**



# Chemistry Review Data Sheet

1. NDA 21-393
2. REVIEW #: 2
3. REVIEW DATE: 11/21/03
4. REVIEWER: Bart Ho
5. PREVIOUS DOCUMENTS:

Original	16-October-01
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6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 1	30-June-03
Amendment 2	20-Nov.-03

7. NAME & ADDRESS OF APPLICANT:

Name: Whitehall-Robins

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

Representative: Mary H. Davis, Director, Regulatory Affairs

Telephone: 973-660-5825

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Advil PM Liquid-Gels
- b) Non-Proprietary Name (USAN): Ibuprofen/Diphenhydramine HCl
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 4
  - Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

505(b)

10. PHARMACOL. CATEGORY: NSAID

11. DOSAGE FORM: Liquid filled capsules

12. STRENGTH/POTENCY: Ibuprofen, 200 mg/ Diphenhydramine HCl, 25 mg

13. ROUTE OF ADMINISTRATION: Oral

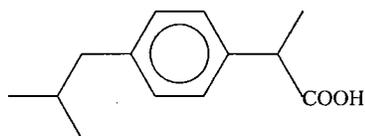
14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

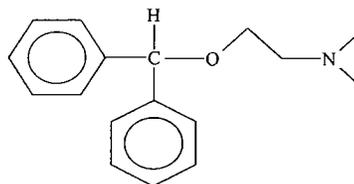
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(±)-2-(p-Isobutylphenyl)propionic acid

Molecular Formula: C<sub>13</sub>H<sub>18</sub>O<sub>2</sub>

Molecular Weight: 206.29



Ethanamine, 2-(diphenylmethoxy)-N,N-dimethyl-, hydrochloride

C<sub>17</sub>H<sub>21</sub>NO.HCl

291.82

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF#	Type	Holder	Item/Component	Code <sup>1</sup>	Status <sup>2</sup>	Date of Review	Comment
/	III	/	/	7	N/A		Safe to use with food
/	III			7	N/A		Safe to use with food
/	III			4	N/A		
/	II			3	Adequate	1/7/03	
/	IV			4	N/A		
/	II			7	N/A		See note 1
/	II			1	Adequate	4/16/02	



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

<sup>1</sup>Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

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")

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

Note #1:

The only information contained in DMF #          that is not submitted in the NDA are         . The rest of the information is contained in the NDA. The DMF was therefore not reviewed.

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	44,767 & 56,521	

18. STATUS: None

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable, review #1		
Pharm/Tox	See review #1		
Biopharm	See attached		
LNC	N/A		
Methods Validation	Sent to FDA lab for validation		
OPDRA	N/A		
EA	Categorical Exclusion		
Microbiology	Acceptable, review #1		



# The Chemistry Review for NDA 21-393

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Recommend approval based on the chemistry point of view.

#### 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 Product(s) and Drug Substance(s)

##### 1) Drug Substances

###### Ibuprofen:

The ibuprofen drug substance is manufactured and supplied by \_\_\_\_\_ . Manufacture and control of the drug substance were referenced to the drug master file # \_\_\_\_\_. The drug master file has been recently reviewed and was found adequate. Tests and acceptance criteria meet the requirement of USP.

###### Diphenhydramine HCl:

Diphenhydramine HCl drug substance is manufactured by \_\_\_\_\_ . Manufacture and control of the drug substance were referenced to the drug master file # \_\_\_\_\_. The drug master file has been reviewed and was found adequate. Tests and acceptance criteria meet the requirement of USP.

##### 2) Drug Product

**Advil PM Liquid-Gels**, in a liquigel dosage form, contains 200 mg ibuprofen and 25 mg of diphenhydramine HCl. The gelatin shell contains gelatin \_\_\_\_\_. The \_\_\_\_\_ excipient contained in the formulation is polyethylene glycol. The manufacturing process involves encapsulating a liquid fill in a soft gelatin shell.



There are basically no differences in the formulation proposed for marketing and the formulations on clinical trial. Because the formulation contained in the liquid gel is a solution, particle size of the ibuprofen and diphenhydramine HCl drug substances is irrelevant in this case.

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

The dosage form, **Advil PM Liquid-Gels**, is a liquigel that contains ibuprofen, 200 mg and diphenhydramine HCl, 25 mg. The product is orally administered and is a night time pain reliever/sleep aid. For adults, the recommend dose is two capsules at bedtime in 24 hours. The product is not intended for children under 12

The combination of ibuprofen and diphenhydramine HCl is a new combination in the analgesic sleep-aid category. The firm considers the drug product to be safe and non-habit-forming.

With the submission of satisfactory stability data in blister packs, Wyeth's requested 24 months expiration period for drug product stored in blister packs at room temperature (25°C/60% RH) is acceptable.

**C. Basis for Approvability or Not-Approval Recommendation**

We recommend approval of NDA 21-393 based on the chemistry point of view. The firm has revised its drug product specifications for unspecified impurities and total unspecified impurities related to diphenhydramine based on ICH threshold for identification not qualification.

Satisfactory months room temperature stability data on a total of batches with the drug product stored in blister packs are provided. Additional stability data submitted indicated that the drug product was stable for the period studied when stored in the proposed container/closure systems. Little or no trend of degradation, other than one degradant, was found. The amount of present in the drug product initially was below Increases over the storage period remain below which is negligible.

; therefore, no toxicity issues are involved with the presence of potencies in both drug substances again varied with storage; however, there was no evidence that a trend in decreasing in potencies existed for the period studied.

Gelatin for Liquid-Gels has been certified to be BSE free.



## CHEMISTRY REVIEW



### Chemistry Assessment Section

Dissolution tests that employed a rotational speed of 150 RPM seemed excessive. Wyeth's proposed dissolution criterion of not less than  $Q$  in 45 minutes did not agree with the actual test results. All stability samples achieved almost 100% dissolution in 30 minutes. BioPharm proposed an interim specification of  $Q = \text{---}$  at 45 minutes for both active components—Ibuprofen and Diphenhydramine HCl—until more data is available on stability of the test product.

The drug product is packaged in a blister packaging unit. All packaging components are deemed adequate previously for protecting the drug product during the shelf-life.

For more information, please see review #1 for details.

### III. Administrative

- A. Reviewer's Signature: N/A
- B. Endorsement Block: N/A
- C. CC Block N/A

11 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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this page is the manifestation of the electronic signature.**  
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/s/

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Bartholomew Ho  
11/21/03 02:29:17 PM  
CHEMIST

John Smith  
11/21/03 02:47:26 PM  
CHEMIST

**NDA 21-393**

**Advil PM Liquid-Gels**

**Whitehall-Robins**

**Bart Ho  
HFD-550  
HFD-560**

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# Chemistry Review Data Sheet

1. NDA 21-393
2. REVIEW #: 1
3. REVIEW DATE: 07/02/02
4. REVIEWER: Bart Ho
5. PREVIOUS DOCUMENTS:

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed  
Original

Document Date  
10-16-01

7. NAME & ADDRESS OF APPLICANT:

Name: Whitehall-Robins

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

Representative: Mary H. Davis, Director, Regulatory Affairs

Telephone: 973-660-5825

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Advil PM Liquid-Gels

b) Non-Proprietary Name (USAN): Ibuprofen/Diphenhydramine HCl

c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

505(b)

10. PHARMACOL. CATEGORY: NSAID

11. DOSAGE FORM: Liquid filled capsules

12. STRENGTH/POTENCY: Ibuprofen, 200 mg/ Diphenhydramine HCl, 25 mg

13. ROUTE OF ADMINISTRATION: Oral

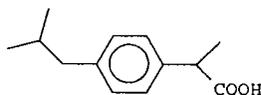
14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note20]:

SPOTS product – Form Completed

Not a SPOTS product

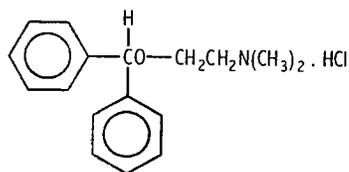
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(±)-2-(p-Isobutylphenyl)propionic acid

Molecular Formula: C<sub>13</sub>H<sub>18</sub>O<sub>2</sub>

Molecular Weight: 206.29



Ethanamine, 2-(diphenylmethoxy)-N,N-dimethyl-, hydrochloride

C<sub>17</sub>H<sub>21</sub>NO.HCl

291.82

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF#	Type	Holder	Item/Component	Code <sup>1</sup>	Status <sup>2</sup>	Date of Review	Comment
	III		/	7	N/A	2-15-02	Safe to use with food
	III			7	N/A	2-15-02	Safe to use with food
	III			4	N/A		
	II			3	Adequate	10/30/96	
	IV			7	N/A		See note 1
	II			7	N/A		See note 2
	II			1	Adequate	4/16/02	

<sup>1</sup>Action codes for DMF Table:

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

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")

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

Note #1:

Information provided in the NDA is sufficient. The color is FDA certified. A detailed review was not performed.

Note #2:

The only information contained in DMF # — that is not submitted in the NDA are

— . The rest of the information is contained in the NDA. The DMF was therefore not reviewed.

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	44,767 & 56,521	

18. STATUS: None

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

# The Chemistry Review for NDA 21-393

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 21-393 is approvable based on the chemistry point of view. Deficiencies listed at the end of this review should be sent to the sponsor for response.

#### 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 Product(s) and Drug Substance(s)

##### 1) Drug Substances

###### Ibuprofen:

The ibuprofen drug substance is manufactured and supplied by \_\_\_\_\_ . Manufacture and control of the drug substance were referenced to the drug master file \_\_\_\_\_ . The drug master file has been recently reviewed and was found adequate. Tests and acceptance criteria meet the requirement of USP.

###### Diphenhydramine HCl:

Diphenhydramine HCl drug substance is manufactured by \_\_\_\_\_ . Manufacture and control of the drug substance were referenced to the drug master file # \_\_\_\_\_ . The drug master file has been reviewed and was found adequate. Tests and acceptance criteria meet the requirement of USP.

##### 2) Drug Product

**Advil PM Liquid-Gels**, in a liquigel dosage form, contains 200 mg ibuprofen and 25 mg of diphenhydramine HCl. The gelatin shell contains gelatin and \_\_\_\_\_ . The \_\_\_\_\_ excipient contained in the formulation is polyethylene glycol. The manufacturing process involves encapsulating a liquid fill in a soft gelatin shell.

## CHEMISTRY REVIEW

### Chemistry Assessment Section

There are basically no differences in the formulation proposed for marketing and the formulations on clinical trial. Because the formulation contained in the liquid gel is a solution, particle size of the ibuprofen and diphenhydramine HCl drug substances is irrelevant in this case.

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

The dosage form of the drug product, **Advil PM Liquid-Gels**, is a liquigel that contains ibuprofen, 200 mg and diphenhydramine HCl 25 mg. The product is orally administered and is a night time pain reliever/sleep aid. The combination of ibuprofen and diphenhydramine HCl is a new combination in the analgesic sleep-aid category. Firm considers the drug product to be safe and non-habit-forming.

#### C. Basis for Approvability or Not-Approval Recommendation

Release and stability tests (and acceptance criteria) were established to assure the drug product quality. A total of \_\_\_\_\_ batches with drug products stored in blister packs are on stability program: \_\_\_\_\_ room temperature stability data on \_\_\_\_\_ batches and \_\_\_\_\_ stability data on the remaining \_\_\_\_\_ batches were provided. Stability data indicated that the drug product was stable for the period studied when stored in the proposed container/closure systems. Little or no degradation, other than one degradant, \_\_\_\_\_, was found. When the drug product was stored at room temperature, degradants of \_\_\_\_\_ were increased from \_\_\_\_\_ at the initial up to \_\_\_\_\_ at the end of \_\_\_\_\_. Potencies varied; however, there was no evidence that a trend in decreasing in potency existed for the period studied. Firm is requesting 24 months expiration date for drug product stored in blister packs at room temperature (25°C/60% RH). Firm's submission of \_\_\_\_\_ room temperature stability data on three batches is not enough to warrant 24 months expiration date. We will request the firm to change the expiration date to \_\_\_\_\_.

All stability samples achieved almost 100% dissolution in 30 minutes. Proposed dissolution criterion of not less than \_\_\_\_\_ (Q) in 45 minutes did not agree with the actual test results. Stability data also indicated that known impurities found in the drug product were minimal. Currently proposed criteria for the known impurities derived from ibuprofen and diphenhydramine HCl failed to reflect the actual results. Tests and specifications for unknown impurities, individual or total, were not provided. Limits for the presence of \_\_\_\_\_ which are known toxicants, should be provided.

## CHEMISTRY REVIEW

### Chemistry Assessment Section

The drug product is packaged in a blister packaging unit. All packaging components are deemed adequate for protecting the drug product during the shelf-life.

Ibuprofen drug substance is manufactured by \_\_\_\_\_ and diphenhydramine HCl is manufactured and supplied by \_\_\_\_\_. The drug product for commercial distribution, **Advil PM Liquid-Gels**, is manufactured, tested and packaged at R.P. Scherer, 2725 Scherer Dr., St. Petersburg, FL 33716. All the facilities specified in the application have been inspected by the compliance and were found acceptable.

NDA 21-393 is approvable at the present time. Additional information requested in this review should be provided.

### III. Administrative

A. Reviewer's Signature N/A

B. Endorsement Block N/A

C. CC Block N/A

40 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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this page is the manifestation of the electronic signature.**  
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/s/

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Bartholomew Ho  
7/2/02 12:13:21 PM  
CHEMIST

John Smith  
7/2/02 12:22:47 PM  
CHEMIST

### Attachment to 356h: Establishment Information

The proposed Advil PM Liqui-Gels will be marketed by Whitehall-Robins Healthcare. The product will be manufactured for Whitehall-Robins in bulk by R.P. Scherer in St. Petersburg, FL. Wyeth-Ayerst in Rouses Point, NY will package the bulk product into blisters. Please note that Whitehall-Robins and Wyeth-Ayerst are sister divisions within American Home Products Corporation. Below is a list of the cGMP facilities that are specified for the manufacturing, packaging and control operations for the proposed product:

Address	Function
R.P. Scherer* 2725 Scherer Dr. St. Petersburg, FL 33716	<ul style="list-style-type: none"><li>• Receipt, testing and release of raw materials</li><li>• Manufacturing</li><li>• Quality Control and Release Testing of bulk product</li></ul>
Wyeth-Ayerst** 64 Maple Street Rouses Point, NY 12979	<ul style="list-style-type: none"><li>• Receipt, testing and release of packaging components</li><li>• Packaging (blisters) and Labeling</li><li>• Quality Control and Release Testing of bulk/packaged product</li><li>• Packaged Product Stability Testing</li></ul>
Whitehall-Robins PR&D 1211 Sherwood Avenue Richmond, VA 23220	<ul style="list-style-type: none"><li>• PRD "Accelerated" Stability Testing</li></ul>

(\*) CFN/Establishment Registration Number 1811396

(\*\*) CFN/Establishment Registration Number 1310337

### Statement of Pre-Approval Inspection (PAI) Readiness

The facilities that are specified above for the manufacturing, packaging and control operations for the proposed product will be ready for PAI by December 17, 2001.