

**CENTER FOR DRUG
EVALUATION AND RESEARCH**

Approval Package for:

APPLICATION NUMBER:

74-567

Trade Name: Ibuprohm Cold & Sinus

Generic Name: Ibuprofen / Pseudoephedrine
Hydrochloride Tablets

Sponsor: Ohm Laboratories, Inc.

Approval Date: April 17, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
74-567**

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**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

74-567

APPROVAL LETTER

APR 17 2001

Ohm Laboratories, Inc.
Attention: Shirley Ternyik, U.S. Agent
Ranbaxy Pharmaceuticals, Inc.
600 College Road East
Princeton, NJ 08540

Dear Madam:

This is in reference to your abbreviated new drug application dated October 31, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ibuprohm Cold and Sinus Tablets (Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP), 200 mg and 30 mg, respectively.

Reference is also made to your amendments dated January 30, March 1, and March 28, 2001. *4-12-01 NC [Signature] 4-19-01*

The listed drug product referenced in your application, Advil Cold and Sinus Tablets of Whitehall Laboratories, Inc., is subject to a period of patent protection which expires on October 9, 2004, (Patent No. 4,552,899). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Ibuprohm Cold and Sinus Tablets will not infringe on the patent or that the patent is otherwise invalid. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action is brought prior to the expiration of forty-five (45) days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified the agency that Ohm Laboratories, Inc. (Ohm) complied with the requirements of Section 505(j)(2)(B) of the Act and that as a result Richardson-Vicks, Inc., a subsidiary of the Proctor and Gamble Company, initiated a patent infringement suit against you in the United States District Court for the District of New Jersey (Richardson-Vicks Inc., v. Ohm Laboratories, Inc., Civil Action No. 96-3788 (WHW)). You have also notified the agency that on December 22, 1997, the litigation referenced above was dismissed without prejudice. The Agency also recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act,

during which time FDA was precluded from approving your application has expired.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ibuprofen Cold and sinus Tablets, 200 mg/30 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Advil Cold and Sinus Tablets of Whitehall Laboratories, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Furthermore, we note that Ohm was the first ANDA applicant to submit a substantially complete ANDA containing a Paragraph IV Certification to the '899 patent. Therefore, with this approval Ohm Laboratories, Inc. is eligible for 180-days of generic drug market exclusivity. Such exclusivity will commence on the date Ohm begins commercial marketing of the drug product.

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commenced commercial marketing of this product.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63; No. 214, 59710).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/s/

Gary Buehler 4/17/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-567

Final Printed Labeling

Final Printed Labeling
Ibuprohm® Cold & Sinus
Consumer Information Leaflet

CONSUMER LABELING LEAFLET FOR Ibuprohm Cold & Sinus
PLEASE SAVE THIS FOR FUTURE USE.

Only selected information is listed on the container label.
Therefore, you should keep this sheet for future reference.

Ibuprohm®
Cold & Sinus

APPROVED

APR 17 2001

IBUPROFEN/PSEUDOEPHEDRINE HYDROCHLORIDE TABLETS/CAPLETS*
Pain Reliever/Fever Reducer/Nasal Decongestant
*Capsule-Shaped Tablets

WARNING: ASPIRIN SENSITIVE PATIENTS. Do not take this product if you have had a severe allergic reaction to aspirin, e.g. — asthma, swelling, shock or hives, because even though this product contains no aspirin or salicylates, cross-reactions may occur in patients allergic to aspirin.

INDICATIONS: For temporary relief of symptoms associated with the common cold, sinusitis or flu including nasal congestion, headache, fever, body aches, and pains.

DIRECTIONS: Adults: Take 1 tablet every 4 to 6 hours while symptoms persist. If symptoms do not respond to 1 tablet, 2 tablets may be used but do not exceed 6 tablets in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. Children: Do not give this product to children under 12 years of age except under the advice and supervision of a doctor.

WARNINGS: Do not exceed recommended dosage because at higher doses nervousness, dizziness or sleeplessness may occur. Do not take for colds for more than 7 days or for fever for more than 3 days unless directed by a doctor. If the cold or fever persists or gets worse or if new symptoms occur, consult a doctor. These could be signs of serious illness. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take this product without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK THIS PRODUCT, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. If you are under a doctor's care for any serious condition, consult a doctor before taking this product. Do not take this

product if you have high blood pressure, heart disease, diabetes, thyroid disease or difficulty in urination due to enlargement of the prostate gland, except under the advice and supervision of a doctor.

ALCOHOL WARNING: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take IBUPROFEN or other pain relievers/fever reducers. Ibuprofen may cause stomach bleeding.

DRUG INTERACTION PRECAUTION: Do not use this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for two weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product. Do not combine this product with other non-prescription pain relievers. Do not combine this product with any other ibuprofen-containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE THIS PRODUCT DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

Store at room temperature; avoid excessive heat (40°C, 104°F).

Active Ingredients: Each tablet contains Ibuprofen 200 mg and Pseudoephedrine HCl 30 mg.

MANUFACTURED BY: OHM LABORATORIES, INC.
FRANKLIN PARK, NJ

496081

Revised: 11/98

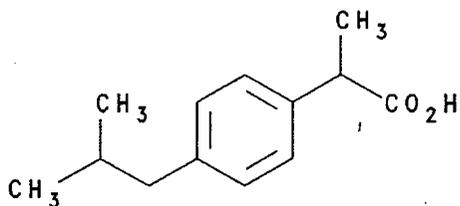
**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

74-567

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 1
2. ANDA 74-567
3. NAME AND ADDRESS OF APPLICANT
 Ohm Laboratories Inc.
 Attention: Arun R. Heble
 P.O. Box 279
 Franklin Park, NJ 08823
6. PROPRIETARY NAME IBUPROHM® COLD & SINUS CAPLETS
7. NONPROPRIETARY NAME
 Ibuprofen and Psuedoephedrine Hydrochloride Tablets
10. PHARMACOLOGICAL CATEGORY NSAID/sinus decongestant
11. Rx or OTC
 Rx
13. DOSAGE FORM Tablets
 (round & capsule-shaped)
14. POTENCY
 200 mg/30 mg
15. CHEMICAL NAME AND STRUCTURE
 Ibuprofen



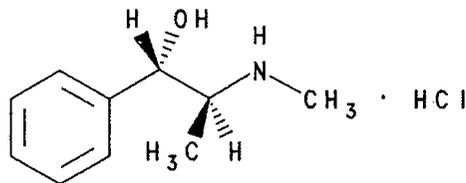
$C_{13}H_{18}O_2$ 206.29

Benzenecarboxylic acid, α -methyl-4-(2-methylpropyl), (\pm)

(\pm)-2-(*p*-Isobutylphenyl)-propionic acid

[15687-27-1]

Pseudoephedrine HCl



$C_{10}H_{15}NO \cdot HCl$ 201.70

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

(+)-Pseudoephedrine hydrochloride

[345-78-8]

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend: NOT APPROVABLE. Major Amendment.

19. REVIEWER: J. L. Smith

DATE COMPLETED:

7/5/95

cc: ANDA
 DUP Jacket
 Division File

Endorsements:

HFD-623/JSmith/
 HFD-623/RKishore/
 C:\WPFILES\ANDAS\N74567R1
 F/T by GP /7/17/95

|S|
 |S|

7-11-95

4. LEGAL BASIS FOR SUBMISSION
NDA 19-771 Advil Cold & Sinus Tablets; Whitehall Labs

Active ingredients, route of administration, dosage form and strength are the same.

Possible problem:

Firm states that the patent for the listed drug - Advil Cold & Sinus Tablets ("Patent No. N19771 001") expired on 09/19/89 and that the exclusivity expired on 09/20/92.

N19771 001 isn't a patent number, it's the NDA number. The current issue of the Orange Book lists patent 4,552,899, which doesn't expire until 11/12/2002.

Note: This patent was added to the Orange Book in the ninth supplement (September 1994) to the 14th edition.

Peter Rickman was advised of the situation on 06/07/95. The question is whether patent 4,552,899 can be considered to be "timely" filed.

5. SUPPLEMENT(s) N/A
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:
- | | |
|------------------------|----------|
| Submitted: | 10/31/94 |
| Refuse To File Letter: | 12/21/94 |
| Amended: | 01/24/95 |
| Filed Letter: | 03/10/95 |
12. RELATED IND/NDA/DMF(s)
see DMF checklist

Note: Firm did not provide a complete list of referenced DMFs on its 356h form.

16. RECORDS AND REPORTS N/A
17. COMMENTS

[]

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commercial

information

4. LEGAL BASIS FOR SUBMISSION

NDA 19-771 Advil Cold & Sinus Tablets; Whitehall Labs (of which the parent company, I assume, is Richardson-Vicks Inc. (RVI)).

Active ingredients, route of administration, dosage form and strength are the same.

☞ The patent certification was incorrect in the original submission (def. 1). But:

In the new correspondence dated 05/29/96, the firm amended its patent certification from "paragraph III" certification to "paragraph IV" in order to market the drug product prior to the expiration date of the innovator's patent 4,552,899 (11/12/2002).

RVI filed a patent infringement action against Ohm 45 days after being notified of Ohm's intention (6/28-8/12). Regardless, the review goes on!

9. AMENDMENTS AND OTHER DATES:

Submitted:	10/31/94	
Refuse To File Letter:	12/21/94	
Amended:	01/24/95	
Filed Letter:	03/10/95	
NA Letter:	07/25/95	
Amendment:	05/06/96	***THIS REVIEW***
New Correspondence:	05/29/96	(Change in patent certification.)

12. RELATED IND/NDA/DMF(s)
see DMF checklist

☞ Note: Firm did not provide a complete list of referenced DMFs on its original 356h form (def. 17); the firm provided a DMF list in the 05/06/96 amendment.

16. RECORDS AND REPORTS N/A17. COMMENTS

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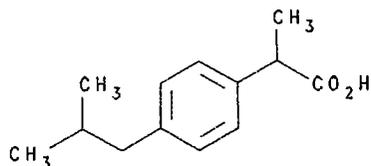
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information

1. CHEMISTRY REVIEW NO 3 2. ANDA 74-567
3. NAME AND ADDRESS OF APPLICANT
 Ohm Laboratories Inc.
 Attention: Arun R. Heble
 P.O. Box 279
 Franklin Park, NJ 08823
4. LEGAL BASIS FOR SUBMISSION 5. SUPPLEMENT(s)
 see next page N/A
6. PROPRIETARY NAME IBUPROHM® COLD & SINUS CAPLETS
7. NONPROPRIETARY NAME
 Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES: see next page

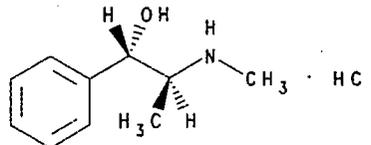
10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC
 NSAID/sinus decongestant Rx
13. DOSAGE FORM 14. POTENCY
 Tablets 200 mg/30 mg
 (round & capsule-shaped)

15. CHEMICAL NAME AND STRUCTURE



$C_{13}H_{18}O_2$ 206.29
 Benzeneacetic acid, α -methyl-
 4-(2-methylpropyl), (\pm)
 (\pm)-2-(*p*-Isobutylphenyl)-
 propionic acid
 [15687-27-1]

Pseudoephedrine HCl



$C_{10}H_{15}NO \cdot HCl$ 201.70
 Benzenemethanol, α -[1-(methylamino)-
 ethyl]-, [S-(R*,R*)]-hydrochloride
 (+)-Pseudoephedrine hydrochloride
 [345-78-8]

18. CONCLUSIONS AND RECOMMENDATIONS
 Recommend: NOT APPROVABLE. ~~Minor~~ ^{Major} Amendment.

19. REVIEWER: J. L. Smith DATE COMPLETED: 07/18/97

4. LEGAL BASIS FOR SUBMISSION

NDA 19-771 Advil Cold & Sinus Tablets; Whitehall Labs (of which the parent company, I assume, is Richardson-Vicks Inc. (RVI)).

Active ingredients, route of administration, dosage form and strength are the same.

In the new correspondence dated 05/29/96, the firm amended its patent certification from "paragraph III" certification to "paragraph IV" in order to market the drug product prior to the expiration date of the innovator's patent 4,552,899 (11/12/2002). RVI filed a patent infringement action against Ohm 45 days after being notified of Ohm's intention.

9. AMENDMENTS AND OTHER DATES:

Submitted:	10/31/94	
Refuse To File Letter:	12/21/94	
Amended:	01/24/95	
Filed Letter:	03/10/95	
NA Letter:	07/25/95	
Amendment:	05/06/96	
New Correspondence:	05/29/96	(Change in patent certification.)
NA Letter:	11/20/96	
New Correspondence?:	01/08/97	(from Keller & Heckman)
Amendment:	02/18/97	***THIS REVIEW***

12. RELATED IND/NDA/DMF(s)
see DMF checklist

16. RECORDS AND REPORTS N/A

17. COMMENTS



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1. CHEMISTRY REVIEW NO: 5 2. ANDA #: 74-567

3. NAME AND ADDRESS OF APPLICANT:

Ohm Laboratories
A Subsidiary of Ranbaxy Pharmaceuticals Inc.
Attention: Ms. Shirley Ternyik
600 College Road East
Princeton, NJ 08540
Telephone No.: 609-720-5612
Fax No.: 609-720-1155

4. LEGAL BASIS FOR SUBMISSION: (As per Review #3)

NDA 19-771 Advil Cold & Sinus Tablets; Whitehall Labs (it is assumed that the parent company is Richardson-Vicks Inc.)

Active ingredients, route of administration, dosage form and strength are the same.

In the new correspondence dated 05/29/96, the firm amended its patent certification from "paragraph III" certification to "paragraph IV" in order to market the drug product prior to the expiration date of the innovator's patent 4,552,899 (11/12/2002). RVI filed a patent infringement action against Ohm 45 days after being notified of Ohm's intention.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: IBUPROHM[®] COLD & SINUS CAPLETS

7. NONPROPRIETARY NAME:

Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

<i>Original Submission</i>	10/31/94
<i>Refuse To File Letter</i>	12/21/94
<i>Amended</i>	01/24/95
<i>Filed Letter</i>	03/10/95
<i>Major NA Letter #1</i>	07/25/95
<i>Tele-Con</i>	10/13/95
<i>Major Amendment</i>	05/06/96
<i>New Correspondence</i>	05/29/96
<i>(Change in patent certification.)</i>	

<i>Major NA Letter #2</i>	11/20/96	
<i>New Correspondence</i>	01/08/97	<i>(from Keller & Heckman)</i>
<i>Major Amendment</i>	02/18/97	
<i>Major NA Letter #3</i>	08/04/97	
<i>FDA Meeting with Ohm</i>	09/18/97	
<i>Major Amendment</i>	01-16-98	
<i>Minor Amendment</i>	11-23-98	- This Review
<i>Fax Amendment</i>	03-12-99	- This Review
<i>Telephone Amendment</i>	04-16-99	- This Review
<i>Telephone Amendment</i>	05-20-99	

10. PHARMACOLOGICAL CATEGORY: NSAID/sinus decongestant
11. R_x or OTC:
R_x
12. RELATED IND/NDA/DMF(s): See DMF checklist.
13. DOSAGE FORM:
Tablets
(Sugar-coated, round & capsule-shaped)
14. POTENCY:
200 mg/30 mg
15. CHEMICAL NAME AND STRUCTURE:
Ibuprofen Pseudoephedrine HCl

C₁₃H₁₈O₂ 206.29
Benzenecetic acid, α-methyl-
4-(2-methylpropyl), (±)

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

[15687-27-1]

C₁₀H₁₅NO•HCl 201.70
Benzenemethanol, α-[1-(methyl-
amino)ethyl]-, [S-(R*,R*)]-
hydrochloride

(+)-Pseudoephedrine hydrochloride

[345-78-8]

16. RECORDS AND REPORTS: N/A

17. COMMENTS: This application was transferred from M. Maust.

=====

FIRM'S RESPONSE (12-MAR-99) TO
FDA TELEPHONE CALL DATED 05-MAR-99

[]

FIRM'S RESPONSE (23-NOV-98) TO
FDA MINOR DEFICIENCY LETTER DATED 28-SEP-98

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OFFICE OF GENERIC DRUGS
ABBREVIATE NEW DRUG APPLICATION

ADDENDUM TO CHEMISTRY REVIEW #5

ANDA: 74-567

DRUG PRODUCT: Ibuprofen and Pseudoephedrine Hydrochloride

FIRM: Ohm Laboratories

DOSAGE FORM: Tablets (Capsule-shaped)

STRENGTH: 200 mg/30 mg

During FDA inspections of the



Conclusion: The application is approvable pending resolution of the above mentioned cGMP issues.

CHEMIST: David J. Cummings DATE: June 3, 1999

cc: ANDA 74-567
ANDA 74-567 (DUP)
DIV FILE
Field Copy

Endorsements:

HFD-623/DJCummings/ *[Signature]*
HFD-623/VSayed, Ph.D. *[Signature]*
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114-363/09
5/3/99

OFFICE OF GENERIC DRUGS
CENTER for DRUG EVALUATION and RESEARCH

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP

1. CHEMISTRY REVIEW NO: 6 2. ANDA #: 74-567
3. NAME AND ADDRESS OF APPLICANT:

Ohm Laboratories
A Subsidiary of Ranbaxy Pharmaceuticals Inc.
Attention: Ms. Shirley Ternyik
600 College Road East
Princeton, NJ 08540
Telephone No.: 609-720-5612
Fax No.: 609-720-1155

4. LEGAL BASIS FOR SUBMISSION: (As per Review #3)
NDA 19-771 Advil Cold & Sinus® Caplets (Whitehall-Robins)

Active ingredients, route of administration, dosage form and strength are the same.

In the new correspondence dated 05/29/96, the firm amended its patent certification from "paragraph III" certification to "paragraph IV" in order to market the drug product prior to the expiration date of the innovator's patent 4,552,899 (11/12/2002). RVI filed a patent infringement action against Ohm 45 days after being notified of Ohm's intention.

Updated information, Feb 7, 2000

In the letter dated May 3, 2000, the firm informed the FDA that the law suit by Whitehall Laboratories was voluntarily dismissed without prejudice on December 22, 1997. The six-month pediatric exclusivity and 30-month stay that resulted from filing of a patent infringement have long been expired (see letter by J.R. Deshmukh to G. Bueller, 5/3/00). The firm believes that the firm is entitled for a 180 days of exclusivity under paragraph IV certification for a generic version of Advil Cold and Sinus tablets.

5. SUPPLEMENT(s): N/A
6. PROPRIETARY NAME: IBUPROHM[®] COLD & SINUS CAPLETS
7. NONPROPRIETARY NAME:
Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:

Original Submission	10/31/94	
Refuse To File Letter	12/21/94	
Amended	01/24/95	
Filed Letter	03/10/95	
Major NA Letter #1	07/25/95	
Tele-Con	10/13/95	
Major Amendment	05/06/96	
New Correspondence	05/29/96	
(Change in patent certification.)		
Major NA Letter #2	11/20/96	
New Correspondence	01/08/97	
Major Amendment	02/18/97	
Major NA Letter #3	08/04/97	
FDA Meeting with Ohm	09/18/97	
Major Amendment	01-16-98	
Minor Amendment	11-23-98	
Fax Amendment	03-12-99	
Telephone Amendment	04-16-99	
Telephone Amendment	05-20-99	
Minor Amendment	02-07-00	This review
Additional Information to minor Amendment	03-10-00	This Review
Controlled Correspondence	05-16-00	This Review
Additional Information to minor Amendment	06-13-00	This Review
10. PHARMACOLOGICAL CATEGORY: NSAID/sinus decongestant
11. R_x or OTC:
R_x
12. RELATED IND/NDA/DMF(s): See DMF checklist.

13. DOSAGE FORM:
 Tablets
 (Sugar-coated, round & capsule-shaped)
14. POTENCY:
 200 mg/30 mg

15. CHEMICAL NAME AND STRUCTURE:

Ibuprofen

Pseudoephedrine HCl

C₁₃H₁₈O₂ 206.29
 Benzeneacetic acid, α-methyl-
 4-(2-methylpropyl), (±)
 (±)-2-(p-
 Isobutylphenyl)propionic acid
 [15687-27-1]

C₁₀H₁₅NO•HCl 201.70
 Benzenemethanol, α-[1-
 (methylamino)ethyl]-, [S-(R*,R*)]-
 hydrochloride
 (+)-Pseudoephedrine hydrochloride
 [345-78-8]

16. RECORDS AND REPORTS: N/A

17. COMMENTS:

1. This application was transferred from M. Maust.
2. Review #6 is done in response to applicant's amendment dated February 7, 2000. This amendment deals with qualification of an ~~_____~~ Previously used ~~_____~~ is unacceptable due to compliance issues.
3. Please refer to review #5 or earlier reviews for additional information. Some information found in previous reviews may not be found in this review.

18. CONCLUSIONS AND RECOMMENDATIONS: **Not Approvable**

19. REVIEWER: Raj Bykadi Ph.D. DATE COMPLETED: 8-4-00

cc: ANDA 74-567
ANANDA 74-567 (DUP)
DIV FILE
Field Copy

Endorsements:

HFD-623/R. Bykadi, Ph.D./8/15/00
HFD-623/A. Mueller, Ph.D./8/15/00

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F/T By: gp/9/8/00

CHEMISTRY REVIEW - NOT APPROVABLE

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OFFICE OF GENERIC DRUGS
CENTER for DRUG EVALUATION and RESEARCH

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP

1. CHEMISTRY REVIEW NO: 7 2. ANDA #: 74-567

3. NAME AND ADDRESS OF APPLICANT:

Ohm Laboratories
A Subsidiary of Ranbaxy Pharmaceuticals Inc.
Attention: Ms. Shirley Ternyik
600 College Road East
Princeton, NJ 08540
Telephone No.: 609-720-5612
Fax No.: 609-720-1155

4. LEGAL BASIS FOR SUBMISSION: (As per Review #3)
NDA 19-771 Advil Cold & Sinus® Caplets (Whitehall-Robins)

Active ingredients, route of administration, dosage form and strength are the same.

In the new correspondence dated 05/29/96, the firm amended its patent certification from "paragraph III" certification to "paragraph IV" in order to market the drug product prior to the expiration date of the innovator's patent 4,552,899 (11/12/2002). RVI filed a patent infringement action against Ohm 45 days after being notified of Ohm's intention.

Updated information, Feb 7, 2000

In the letter dated May 3, 2000, the firm informed the FDA that the law suit by Whitehall Laboratories was voluntarily dismissed without prejudice on December 22, 1997. The six-month pediatric exclusivity and 30-month stay that resulted from filing of a patent infringement have long been expired (see letter by J.R. Deshmukh to G. Buehler, 5/3/00). The firm believes that the firm is entitled to a 180 days of exclusivity under paragraph IV certification for a generic version of Advil Cold and Sinus tablets.

- 5. SUPPLEMENT (s): N/A
- 6. PROPRIETARY NAME: IBUPROHM[®] COLD & SINUS CAPLETS
- 7. NONPROPRIETARY NAME:
Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP
- 8. SUPPLEMENT (s) PROVIDE (s) FOR: N/A

- 9. AMENDMENTS AND OTHER DATES:
 Original Submission 10/31/94
 Refuse To File Letter 12/21/94
 Amended 01/24/95
 Filed Letter 03/10/95
 Major NA Letter #1 07/25/95
 Tele-Con 10/13/95
 Major Amendment 05/06/96
 New Correspondence 05/29/96
 (Change in patent certification.)

- Major NA Letter #2 11/20/96
- New Correspondence 01/08/97
- Major Amendment 02/18/97
- Major NA Letter #3 08/04/97
- FDA Meeting with Ohm 09/18/97
- Major Amendment 01-16-98
- Minor Amendment 11-23-98
- Fax Amendment 03-12-99
- Telephone Amendment 04-16-99
- Telephone Amendment 05-20-99
- Minor Amendment 02-07-00
- Additional Information to minor Amendment 03-10-00
- Controlled Correspondence 05-16-00
- Additional Information to minor Amendment 06-13-00

Minor Amendment 10-26-00 This review

- 10. PHARMACOLOGICAL CATEGORY:
NSAID/sinus decongestant
- 11. R_x or OTC:
OTC

18. CONCLUSIONS AND RECOMMENDATIONS: **Not Approvable**

19. REVIEWER: Raj Bykadi Ph.D. DATE COMPLETED: 11/9/00

cc: ANDA 74-567
ANDA 74-567 (DUP)
DIV FILE
Field Copy

Endorsements:

HFD-623/R. Bykadi, Ph.D./11/9/00 11/14/00
HFD-623/A. Mueller, Ph.D./11/9/00 11/14/00

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F/T By: gp/11/26/00

CHEMISTRY REVIEW - NOT APPROVABLE

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11-27-00
28-00

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ON ORIGINAL**

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OFFICE OF GENERIC DRUGS
CENTER for DRUG EVALUATION and RESEARCH

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP

1. CHEMISTRY REVIEW NO: 8 2. ANDA #: 74-567
3. NAME AND ADDRESS OF APPLICANT:

Ohm Laboratories
A Subsidiary of Ranbaxy Pharmaceuticals Inc.
Attention: Ms. Shirley Ternyik
600 College Road East
Princeton, NJ 08540
Telephone No.: 609-720-5612
Fax No.: 609-720-1155

4. LEGAL BASIS FOR SUBMISSION:
NDA 19-771 Advil Cold & Sinus® Caplets (Whitehall-Robins)

Active ingredients, route of administration, dosage form and strength are the same.

In the new correspondence dated 05/29/96, the firm amended its patent certification from "paragraph III" certification to "paragraph IV" in order to market the drug product prior to the expiration date of the innovator's patent 4,552,899 (11/12/2002). RVI filed a patent infringement action against Ohm 45 days after being notified of Ohm's intention.

Updated information, Feb 7, 2000

In the letter dated May 3, 2000, the firm informed the FDA that the law suit by Whitehall Laboratories was voluntarily dismissed without prejudice on December 22, 1997. The six-month pediatric exclusivity and 30-month stay that resulted from filing of a patent infringement have long been expired (see letter by J.R. Deshmukh to G. Buehler, 5/3/00). The firm believes that the firm is entitled to a 180 days of exclusivity under paragraph IV certification for a generic version of Advil Cold and Sinus tablets.

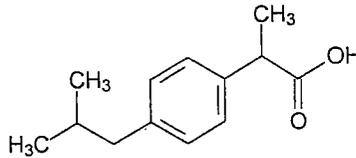
- 5. SUPPLEMENT(s): N/A
- 6. PROPRIETARY NAME: IBUPROHM® COLD & SINUS CAPLETS
- 7. NONPROPRIETARY NAME:
Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP
- 8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
- 9. AMENDMENTS AND OTHER DATES:

Original Submission	10/31/94
Refuse To File Letter	12/21/94
Amended	01/24/95
Filed Letter	03/10/95
Major NA Letter #1	07/25/95
Tele-Con	10/13/95
Major Amendment	05/06/96
New Correspondence	05/29/96
(Change in patent certification)	
Major NA Letter #2	11/20/96
New Correspondence	01/08/97
Major Amendment	02/18/97
Major NA Letter #3	08/04/97
FDA Meeting with Ohm	09/18/97
Major Amendment	01-16-98
Minor Amendment	11-23-98
Fax Amendment	03-12-99
Telephone Amendment	04-16-99
Telephone Amendment	05-20-99
Minor Amendment	02-07-00
Additional	
Information to minor	
Amendment	03-10-00
Controlled	
Correspondence	05-16-00
Additional	
Information to minor	
Amendment	06-13-00
Minor Amendment	10-26-00
Telephone Amendment	03-01-00

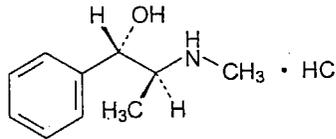
Minor Amendment 01-30-01 This review

10. PHARMACOLOGICAL CATEGORY: NSAID/sinus decongestant
11. R_x or OTC: OTC
12. RELATED IND/NDA/DMF(s): See DMF checklist.
13. DOSAGE FORM: Tablets
(Sugar-coated, round & capsule-shaped)
14. POTENCY: 200 mg/30 mg
15. CHEMICAL NAME AND STRUCTURE:

Ibuprofen



Pseudoephedrine HCl



Ibuprofen

C₁₃H₁₈O₂ 206.29
Benzeneacetic acid, α-methyl-
4-(2-methylpropyl), (±)

(±)-2-(p-
Isobutylphenyl)propionic acid
[15687-27-1]

Pseudoephedrine HCl

C₁₀H₁₅NO·HCl 201.70
Benzenemethanol, α-[1-
(methylamino)ethyl]-, [S-(R*,R*)]-
hydrochloride

(+)-Pseudoephedrine hydrochloride

[345-78-8]

16. RECORDS AND REPORTS: N/A

- 17. COMMENTS:
See previous reviews for any additional information. The Application is approvable.
- 18. CONCLUSIONS AND RECOMMENDATIONS: **Approvable**
- 19. REVIEWER: Raj Bykadi Ph.D. DATE COMPLETED: Feb 8, 2001

cc: ANDA 74-567
ANANDA 74-567 (DUP)
DIV FILE
Field Copy

Endorsements:

HFD-623/R. Bykadi, Ph.D. Feb 8, 2001/3/2/01

HFD-623/A. Mueller, Ph.D./ Feb 8, 2001/3/2/01

[S] - 4-4-01
[S] - 4-4-01

F/T By: DJ 4/4/01

CHEMISTRY REVIEW - APPROVABLE

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MINOR AMENDMENT

SEP 21 2000

ANDA 74-567

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



TO: APPLICANT: Ohm Laboratories

TEL: 609 720 5612

ATTN: Shirley Ternyik

FAX: 609 720 1155

FROM: Joseph Buccine

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated October 31, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen and Pseudoephedrine HCl Tablets USP.

Reference is also made to your amendment(s) dated: February 7 and June 13, 2000.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments are provided.

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**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

74-567

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74 567

SPONSOR: OHM LABS INC

DRUG & DOSAGE FORM: IBUPROFEN / PSEUDOPHEDRINE HCl TAB

STRENGTH/(s): 200 mg / 30 mg

TYPE OF STUDY: Single/Multiple

Fasting/✓ Food ✓

STUDY SITE: _____

STUDY SUMMARY:	FASTING		NON FASTING		RATIO
	IBUPR	PSE	IBUPR	PSE	
C _{max}					1.00
AUC (0-∞)	111/112 (97-104)	1983/1979 (96-107)	107/105		1.02
T _{max}	1.5/1.4	2.2/1.69	1.7/1.5		0.97
T _{1/2}	1.9/1.9	5.5/5.2	2/2.2		0.94

RATIO
0.95

DISSOLUTION:

IBU

PSE

30 MIN
30 MIN

Q = NLT IN 30 MINS FOR BOTH

TEST REF.

PRIMARY REVIEWER: _____

BRANCH: 2

INITIAL: ISI

DATE: 7/21/1995

BRANCH CHIEF: _____

BRANCH: 2

INITIAL: ISI

DATE: 7/21/95

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: ISI

DATE: 9/12/95

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: ISI

DATE: 9/14/95

SEP 6 1995

Ibuprofen/Pseudoephedrine HCl
200 mg/30 mg Tablet
ANDA # : 74-567
Reviewer : S.G.Nerurkar
A74567SD.094

Ohm Labs. Inc.
Franklin Park, NJ
Submission Date :
October 31, 1994

REVIEW OF BIOEQUIVALENCE STUDY

Background Information :

This is a first generic drug application for an OTC drug product. The "Orange Book" list Advil^R Cold and Sinus (formerly CoAdvil) from Whitehall Labs as the listed reference drug product (NDA 19-771) which was approved on September 19, 1989. There is also another innovator entry named Sine-Aid IB, in the "Orange Book" from McNeil Cons. Prods (NDA 19-899) which was approved on December 31, 1992. Sine-Aid IB was approved by Pilot Drug Evaluation Staff (HFD 7). In our files, we do not have guideline for this drug product. Therefore, information from the following sources was used.

- 1) USP 2), PDR 3) Ms. Nguyen's review of _____
from _____
- Biopharmaceutics) review of Sine-Aid IB from McNeil (NDA 19899),
- 4) The Literature Search and 5) Dr. Makary's review of _____

_____ The pertinent information is summarized below (the details are shown at the end of the text).

Ibuprofen, an NSAID, is a racemate(S + R) and Pseudoephedrine HCl, (PSE) a sympathomimetic drug, is single dextrorotatory enantiomer. The PDR has pharmacokinetic (PK) information on ibuprofen but not on PSE. The Division of Bioequivalence files have reviews on many ANDAs for immediate release, ibuprofen, 200 mg tablet. The ibuprofen PK information from those reviews are consistent. A 200 mg dose of ibuprofen on empty stomach produced AUC(0-T) of 75 mcgxhr/ml, AUC(0-inf) of 81 mcgxhr/ml and Cmax of 25 mcg/ml at Tmax of 1.1-1.35 hr. A blood collection of 15 hours which was adequate considering the halflife of 2hr. The ibuprofen dosed (200 mg) under non-fasting conditions in second study produced AUC(0-T) of 71-80 mcgxhr/ml, AUC(0-inf) of 80-81 mcgxhr/ml and Cmax of 17 mcgxhr/ml at Tmax of 2 hr. Half-life was 2.4-2.6 hr in the non-fasting study. A 30 mg dose of PSE on empty stomach produced AUC(0-T) of 1000 ngxhr/ml, AUC(0-inf) of 1200 ngxhr/ml and Cmax of 100 ng/ml at Tmax of 1.5-2 hr. A blood collection of 36 hours which was adequate considering the half-life of 7 hrs. Ibuprofen has 2 major (2-

hydroxy and 2-carboxy) inactive metabolites and PSE has only one active metabolite, norPSE (6 % of the dosed PSE is converted to norPSE). None of these metabolites were measured in any of the studies submitted to the Agency.

Conclusion : Two separate (A fasting and a non-fasting) studies are necessary. There is no need to measure metabolites and enantiomers of ibuprofen as well as metabolites of PSE. Because of the half-life of PSE, the blood collection should be carried out till 36 hours and not upto 24 hours.

**APPEARS THIS WAY
ON ORIGINAL**

IN VIVO SINGLE DOSE, FASTING BIOEQUIVALENCE STUDY

Project # : 940340

Objective : To compare the bioavailability of the test drug product with the reference drug product under fasting condition.

Investigators : _____

Design : Randomized, single dose, fasting, 2-treatment, 2-period, 2-sequence, crossover study with 7-day washout period.

Study Dates : Clinical Part : 4-13-1994 to 4-23-1994
Analytical Part : 5-18-1994 to 6-6-1994
Max. storage of samples : 53 days at -22°C
Documented stability : 148 days

Subject Selection : Normal, healthy, 26 male subjects between the ages of 19 to 45 years and body weight \pm 15% of the ideal body weight completed the study. They were screened for medical history, blood chemistry, hematology, urinalysis and vital signs. They were without any obvious somatic (cardiovascular, pulmonary, hepatic, renal, hematological, GI, immunological, endocrine, neurological) disorders. None of them had i) allergy to ibuprofen and PSE, ii) been on abnormal diet during four prestudy weeks, iii) participated in a clinical study or in blood donation for 28 days prior to study and iv) history of alcohol or drug abuse within one year of the study.

Subject
Preparation :

The subject were kept in the clinical facility from 12 hours pre dose to 36 hours post dose. They were asked not to i) take any medication 7 days prior to the study, ii) consume alcohol or xanthine containing food or drinks 24 hours prior to the study, iii) smoke 1 hour before and 2 hours after the dosing. On the eve of the study they fasted overnight for 10-12 hours and 4 hours after the dosing.

Drug administration After an overnight fast, each subject received a 400 mg/60 mg single dose (test or reference) of Ibuprofen/Pseudoephedrine HCl (2x200 mg/30 mg Tab) with 240 ml of water. No water and food was allowed 4 hours post dose. They were asked not to lie down for 4 hours. A standardized diet was provided at the scheduled times.

Drug Information :

A = test drug Product [Ibuprohm (Cold & Sinus)]. 200mg/30mg Ibuprofen/Pseudoephedrine HCl Tablet, from OHM Labs. Inc. Brown, sugar coated, oval (capsule shaped), tablet with "424" encircled and printed in black on one side and plain other side.

Lot # 13527, Lot size units,
Average tablet weight = 545.8 mg (range 520-567 mg)
Potency for Ibuprofen = 100% and PSE = 97.1%
Content Uniformity Ibuprofen = 101.6% (%CV=2.02) and PSE = 99.2%
(%CV=2.39)
Expiry date 7/1995.

B = reference drug Product. Advil^R Cold and Sinus, 200mg/30mg Ibuprofen/pseudoephedrine HCl Tablet, from Whitehall Labs. Inc. Brown, sugar coated, oval (capsule shaped) tablet with "Advil Cold & Sinus" printed in black on one side and plain other side.
Lot # H225
Average tablet weight = 526.4 mg (range 515.1-540 mg)
Potency for Ibuprofen = 98.9% and PSE = 98.4%
Content Uniformity Ibuprofen = 99.6% (%CV=1.5) and PSE = 99.1%
(%CV=2.4)
Expiry date 5/1995.

Drug Composition :

INGREDIENT

(MG/TABLET)

CORE

1. Ibuprofen, USP	200.00
2. Pseudoephedrine HCl, USP	30.00
3. Powdered Cellulose,	_____
4. Powdered Cellulose,	_____
5. Corn Starch	_____
6. Pregelatinized Starch,	_____
7. Guar Gum,	_____
8. Talc, USP	_____
9. Croscarmellose Na,	_____
10. Crospovidone,	_____
11. SiO ₂ ,	_____
12. Hydrogenated Vegetable Oil,	_____

1. Acasia,	_____
2. CaCO ₃ ,	_____
3. Carnauba Wax,	_____
4. _____	_____
5. _____	_____
6. Corn Starch,	_____
7. Gelatin,	_____
8. Hydroxypropyl Cellulose,	_____
9. _____	_____
10. Kaolin, USP	_____
11. _____	_____
12. Polyethylene Glycol	_____
13. _____	_____
14. Sucrose,	_____
15. Talc, USP	_____
16. White Wax,	_____

TOTAL (TABLET) 545.00

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RESULTS

Ibuprofen

Twenty six subjects completed the study, however, only first 24 subject samples were analyzed as mentioned in the protocol. The firm stated _____ as the LLOQ. Plasma profile of every subject was scanned and it was found that the firm has not reported any value below _____. The lowest value reported was _____ for subject 22 at 12 hours when he received test drug product. The firm did not provide any chromatograms for this subject. However it had provided a pertinent computer print out. The print out showed that subject # 22 who received test ibuprofen, had chromatographic peak value of 166 (ratio = 0.0050) at 12 hours while the peak value for lowest calibration std, _____ was 159 (ratio = 0.0051). Similarly, from the computer print out other chromatographic peak values for the samples, reported as BLQ (subjects #s 3,10,13,15,16 and 17 at 0.25 hours, all except # 15 received reference drug), were scrutinized. They were satisfactory. Unfortunately none of these chromatograms were supplied. Therefore, all the chromatograms in the submission were checked (especially, for zero hour) and they were acceptable.

Individual plasma ibuprofen profile is a very important parameter. This reviewer deems it as an important supplementary information to compare every subject's test-ibuprofen-profile to his reference-ibuprofen-profile. The results are shown below.

Parameter	T > R	R > T	T = R	Descriptor
Pattern	-----	-----	-----	Same (24/24)
Cmax	-----	-----	-----	-----
Tmax	13/24	6/24	5/24	-----

Thus, following important items were evident in this comparison. I) All subjects have similar pattern of plasma profile. ii) Majority of subjects had reference Cmax higher than test Cmax. iii) Majority of subjects had test Tmax higher than reference Tmax. After this comparison, the mean test and reference plasma profiles were compared. The following table shows the comparison.

Table 1 : Mean Plasma Profile for Ibuprofen mcg/ml \pm SD in a Single Dose (2x200mg/60mg), Fasting Study on 200mg/60mg Tablet

Time	Test	(n/24)	Reference	(n/24)	(T/R)
0	0		0		
0.25	3.933 \pm 3.9	23/24	3.453 \pm 4.15	19/24	1.14
0.50	15.87 \pm 7.3		20.69 \pm 11.1		0.77
0.75	20.09 \pm 8.7		25.91 \pm 10.3		0.78
1.00	21.33 \pm 7.8		26.29\pm9.07		0.81
1.25	20.62 \pm 7.0		24.89 \pm 7.11		0.83
1.50	20.96 \pm 5.6		23.97 \pm 6.39		0.87
1.75	22.50\pm6.9		23.41 \pm 6.90		0.96
2.00	22.11 \pm 6.7		22.18 \pm 6.83		1.00
2.50	21.18 \pm 6.1		19.35 \pm 5.93		1.09
3.00	19.59 \pm 5.6		17.95 \pm 5.33		1.09
4.00	14.98 \pm 4.8		13.40 \pm 4.73		1.12
6.00	6.019 \pm 2.2		5.600 \pm 2.28		1.07
8.00	2.919 \pm 1.1		2.796 \pm 1.28		1.04
10.0	1.523 \pm 0.7		1.463 \pm 0.73		1.04
12.0	0.809 \pm 0.3		0.785 \pm 0.39		1.03

(n/24) - Number of subjects out of 24, show measurable ibuprofen.

The mean ibuprofen profiles for the test and reference drug appeared to be similar. The mean reference ibuprofen profile peaked earlier (not Tmax) than the mean test profile (1.00 hr vs. 1.75 hr, see the high-lighted values). The ratio of mean test/reference were above 0.8 at both these times. For antipyresis 10 mcg/ml of plasma ibuprofen, is accepted as therapeutic level in febrile children. From above table it is evident that both drug products maintain that therapeutic ibuprofen levels from 0.5 to 4 hours. Thus, according to this reviewer, the ibuprofen plasma profiles obtained after two treatments appear to be satisfactory. The next step is to compare pharmacokinetic parameters of ibuprofen.

The test AUC(0-T) values for subjects 2, 5 and 20 and reference AUC(0-T) values for subjects 3, 6, 22 were calculated from their plasma ibuprofen profiles. These calculated values were identical to the AUC(0-T) values reported by the firm. Thus, the spot checking showed the reliability of the firm's methods of calculating AUC(0-T) values. The table below shows the pharmacokinetic parameters of ibuprofen and their statistical analysis.

Table 2 : Mean Pharmacokinetic Parameters for Ibuprofen in a Single Dose (2x200mg), Fasting Study on 200mg/60mg Tablet

Parameter	Test Drug	Ref. Drug	Ratio (T/R)	A 90% C.I.	N O V A Effects
Cmax (mcg/ml)	27.18 ±5.19	31.49 ±6.61	0.86		
ln Cmax	3.285 ±0.19	3.426 ±0.23	0.87	80-94	trt
AUC(0-T) mcgxhr/ml	109.10 ±22.37	109.20 ±22.90	1.00		
ln AUC(0-T)	4.669 ±0.23	4.669 ±0.23	1.00	97-104	none
AUC(0-inf) mcgxhr/ml	111.41 ±23.27	111.52 ±23.94	1.00		
ln AUC(0-inf)	4.689 ±0.23	4.689 ±0.24	1.00	97-104	none
Tmax hr	1.531 ±0.75	1.385 ±0.83	1.11		
Half-life hr	1.910 ±0.20	1.926 ±0.28	0.99		

The information in tables 1 and 2 showed that

- i) Cmax, AUC(0-T) and AUC(0-inf) values are acceptable by 90% confidence interval.
- ii) Mean test Cmax (27.18 mcg/ml) and peak value for test mean profile (22.5 mcg/ml - see table 1) are not close (ratio = 1.21). Similarly, reference Cmax (31.49 mcg/ml) and the mean peak value for reference mean profile (26.29 mcg/ml - see table 1) are not close (ratio = 1.20).
- iii) Mean test Tmax (1.531 hr) and time to peak for the test mean profile (1.75 hr - see table 1) are close (ratio = 0.87). while, mean reference Tmax (1.385 hr) and time to peak for the reference mean profile (1.00 hr - see table 1) are not close (ratio = 1.4)
- iv) This discrepancy in Cmax and Tmax values may be attributed to the 2 peaks or a peak and shoulder seen in 19 subjects (10 subjects receiving test drug and 9 subjects receiving reference drug).

Conclusion : Ibuprofen component of the test drug product is bioequivalent to the ibuprofen component of the reference drug product under fasting condition.

Pseudoephedrine HCl (PSE) :

Twenty six subjects completed the study, however, only first 24 subject samples were analyzed as mentioned in the protocol. The firm stated _____ as the LLOQ. Plasma profile of every subject was scanned and it was found that the firm has not reported any value below _____. The lowest value reported was _____ for subject 12 at 0.5 hour when he received test drug product. The firm did not provide any chromatograms for this subject. However it had provided a pertinent computer print out. The print out showed that subject # 12 who received test PSE, had chromatographic peaks ratio of 0.0056 at 0.5 hour while the peaks ratio for lowest calibration std, _____ was 0.0.0059. Similarly, from the computer print out for other chromatographic peaks ratios for the samples, reported as BLQ at time points other than 0.25, 24 and 36 hours [subject # 15 (test) at 0.5 hour, # 22 (test) at 16 hrs, #10 (reference) at 0.5 hr and #s 19 and 22 (reference) at 16 hrs], were scrutinized. They were satisfactory. Unfortunately none of these chromatograms were supplied. Therefore, all the chromatograms in the submission were checked (especially, for zero hour) and they were acceptable.

Individual plasma PSE profile is a very important parameter. It is an important supplementary information to compare every subject's **test-PSE-profile** to his **reference-PSE-profile**. The results are shown below.

Parameter	T > R	R > T	T = R	Descriptor
Pattern	-----	-----	-----	Same (24/24)
Cmax	-----	-----	-----	-----
Tmax	14/24	6/24	4/24	-----

Thus, following important items were evident in this comparison. **i)** All subjects have similar pattern of plasma profile. **ii)** Majority of subjects had reference Cmax higher than test Cmax. **iii)** Majority of subjects had test Tmax higher than reference Tmax. **iv)** This trend is also seen in ibuprofen (see page 7). Subsequent to this comparison, the mean test and reference plasma profiles were compared. The following table shows the comparison.

Table 3 : Mean Plasma Profile for PSE ng/ml \pm SD in a Single Dose (2x60mg), Fasting Study on 200mg/60mg Tablet

Time	Test	(n/24)	Reference	(n/24)	(T/R)
0	0		0		
0.25	1.900 \pm 6.53	2/24	1.800 \pm 6.00	1/24	1.06
0.50	58.43 \pm 41.9		73.79 \pm 54.9	22/24	0.79
0.75	113.4 \pm 54.1		137.3 \pm 48.7		0.83
1.00	133.7 \pm 44.1		166.4 \pm 40.6		0.80
1.25	149.7 \pm 33.7		184.1 \pm 33.5		0.81
1.50	159.3 \pm 25.6		188.3 \pm 29.8		0.85
1.75	167.8 \pm 25.7		186.0 \pm 29.6	23/24	0.90
2.00	172.9 \pm 28.3		192.8\pm36.3		0.90
2.50	176.8\pm28.3		184.7 \pm 33.5		0.96
3.00	173.5 \pm 29.6		176.1 \pm 34.8		0.99
4.00	167.5 \pm 35.3		165.4 \pm 37.1		1.01
6.00	130.5 \pm 31.7		133.2 \pm 35.7		0.98
8.00	109.2 \pm 26.7		105.9 \pm 28.9		1.03
10.0	82.68 \pm 25.0		77.30 \pm 24.1		1.07
12.0	63.05 \pm 22.8		63.52 \pm 20.2		0.99
16.0	40.00 \pm 16.0	22/24	36.52 \pm 16.8	22/24	1.10
24.0	11.47 \pm 9.33	14/24	10.23 \pm 8.80	14/24	1.12
36.0	0.000 \pm 0.00	0/24	0.000 \pm 0.00	0/24	----

(n/24) - Number of subjects out of 24, show measurable PSE.

The mean PSE profiles for the test and reference drug appeared to be similar. The mean reference PSE profile peaked earlier (not Tmax) than the mean test profile (2.00 hr vs. 2.50 hr, see the high-lighted values). The ratio of mean test/reference were above 0.8 at both these times. Thus, according to this reviewer, the PSE plasma profiles obtained after two treatments appear to be satisfactory.

The next step is to compare pharmacokinetic parameters of PSE.

The test AUC(0-T) values for subjects 9, 10 and 15 and reference AUC(0-T) values for subjects 1, 7, 23 were calculated from their plasma PSE profiles. These calculated values were identical to the AUC(0-T) values reported by the firm. Thus, the spot checking showed the reliability of the firm's methods of calculating AUC(0-T) values. The table below shows the pharmacokinetic parameters of PSE and their statistical analysis.

Table 4 : Mean Pharmacokinetic Parameters for PSE in a Single Dose (2x200mg/60mg), Fasting Study on 200mg/60mg Tablet

Parameter	Test Drug	Ref. Drug	Ratio (T/R)	A 90% C.I.	N O V A Effects
Cmax (ng/ml)	200.94 ±26.8	209.56 ±32.9	0.96		
ln Cmax	5.294 ±0.14	5.333 ±0.16	0.96	93-100	none
AUC(0-T) ngxhr/ml	1787.6 ±409.6	1822.4 ±481.2	0.98		
ln AUC(0-T)	7.460 ±0.25	7.470 ±0.30	0.99	94-105	none
AUC(0-inf) mcgxhr/ml	1982.6 ±419.2	1978.9 ±491.1	1.00		
ln AUC(0-inf)	7.570 ±0.23	7.560 ±0.28	1.01	96-107	none
Tmax hr	2.229 ±1.11	1.688 ±0.48	1.32		
Half-life hr	5.525 ±1.14	5.241 ±0.93	1.05		

The information in tables 3 and 4 showed that

i) Cmax, AUC(0-T) and AUC(0-inf) values are acceptable by 90% confidence interval. ii) Mean test Cmax (200.94 ng/ml) and peak value for test mean profile (176.8 ng/ml - see table 3) are moderately apart (ratio = 1.13). While, reference Cmax (209.56 ng/ml) and the mean peak value for reference mean profile (192.75 ng/ml - see table 3) are close (ratio = 1.09). iii) Mean test Tmax (2.229 hr) and time to peak for the test mean profile (2.5 hr - see table 3) are close (ratio = 0.89). Similarly, mean reference Tmax (1.688 hr) and time to peak for the reference mean profile (2.00 hr - see table 3) are also fairly close (ratio = 0.84)

Conclusion : PSE component of the test drug product is bioequivalent to the PSE component of the reference drug product under fasting condition.

THE BIOEQUIVALENCE STUDY UNDER FASTING CONDITION IS ACCEPTABLE.

ADVERSE EVENTS :

Seven out of 14 reported events, were treatment related. Five of these episodes occurred during trt A (test) and two occurred during trt B (reference).

IN VIVO SINGLE DOSE, NON-FASTING BIOEQUIVALENCE STUDY

Project # : 930454

Objective : To compare the bioavailability of the test drug product with the reference drug product under non-fasting condition.

Investigators : _____

Design : Randomized, single dose, non-fasting, 3-treatment, 3-period, 6-sequence, crossover study with 7-day washout periods.

Study Dates : Clinical Part : 1-5-1994 to 1-24-1994
Analytical Part : 1-26-1994 to 3-30-1994
Max. storage of samples : 79 days at -22°C
Documented stability : 144 days

Subject Selection : Normal, healthy, 17 male subjects between the ages of 20 to 42 years and body weight \pm 15% of the ideal body weight completed the study. They were screened for medical history, blood chemistry, hematology, urinalysis and vital signs. They were without any obvious somatic (cardiovascular, pulmonary, hepatic, renal, hematological, GI, immunological, endocrine, neurological) disorders. None of them had **i)** allergy to ibuprofen and PSE, **ii)** been on abnormal diet during four prestudy weeks, **iii)** participated in a clinical study or in blood donation for 28 days prior to study and **iv)** history of alcohol or drug abuse within one year of the study.

Subject The subject were kept in the clinical facility
Preparation : from 12 hours pre dose to 36 hours post dose. They were asked not to i) take any medication 7 days prior to the study, ii) consume alcohol or xanthine containing food or drinks 24 hours prior to the study, iii) smoke 1 hour before and 2 hours after the dosing. One third of the subjects, fasted overnight for 10-12 hours and 4 hours after the dosing. The remaining two third of the subjects, fasted 10-12 hours and ate a standard breakfast before the dosing.

Drug administration After an overnight fast, each subject received a 400 mg/60 mg single dose (test or reference) of Ibuprofen/Pseudoephedrine HCl (2x200 mg/30 mg Tab) with 240 ml of water (some subjects were served breakfast before dosing. for details see "subject preparation" above) . No water and food was allowed 4 hours post dose. They were asked not to lie down for 4 hours. A standardized diet was provided at the scheduled times.

Drug Information :

A = test drug Product [Ibuprohm (Cold & Sinus)]. 200mg/30mg Ibuprofen/Pseudoephedrine HCl Tablet, from OHM Labs. Inc. Brown, sugar coated, oval (capsule shaped), tablet with "424" encircled and printed in black on one side and plain other side.

Lot # 13527, Lot size units,
Average tablet weight = 545.8 mg (range 520-567 mg)
Potency for Ibuprofen = 100% and PSE = 97.1%
Content Uniformity Ibuprofen = 101.6% (%CV=2.02) and PSE = 99.2%
(%CV=2.39)
Expiry date 7/1995.

B = reference drug Product. 200mg/30mg Ibuprofen/pseudoephedrine HCl Tablet, from Whitehall Labs. Inc. Brown, sugar coated(?), oval (capsule shaped) tablet with "Advil Cold & Sinus" printed in black on one side and plain other side.

Lot # H225
Average tablet weight = 526.4 mg (range 515.1-540 mg)
Potency for Ibuprofen = 98.9% and PSE = 98.4%
Content Uniformity Ibuprofen = 99.6% (%CV=1.5) and PSE = 99.1%
(%CV=2.4)
Expiry date 5/1995.

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secret and/or

confidential

commercial

information

After this comparison, the mean test and reference plasma profiles were compared. The following table shows the comparison.

Table 5 : Mean Plasma Profile for Ibuprofen mcg/ml \pm SD in a Single Dose (2x200mg/60mg), Non-fasting Study on 200mg/60mg Tablet

Time	A=Test (fast)	B=Test (fed)	C=Ref. (fed)	B/C	B/A
0	0.130 \pm 0.6	0	0		
0.25	2.890 \pm 3.7	1.420 \pm 4.7	1.220 \pm 2.26	1.16	0.49
0.50	15.82 \pm 7.0	9.710 \pm 10	10.90 \pm 10.5	0.89	0.61
0.75	24.18 \pm 7.8	15.61 \pm 14	18.09 \pm 12.6	0.86	0.68
1.00	26.17 \pm 8.3	20.63 \pm 13	21.96 \pm 10.9	0.94	0.79
1.25	26.44 \pm 8.7	22.59 \pm 10	24.50 \pm 12.5	0.92	0.85
1.50	27.24\pm9.1	24.30\pm7.0	24.85\pm12.0	0.98	0.89
1.75	25.99 \pm 8.0	23.80 \pm 6.1	22.23 \pm 9.83	1.07	0.92
2.00	24.65 \pm 6.3	22.70 \pm 5.1	20.86 \pm 8.14	1.09	0.92
2.50	22.15 \pm 5.5	19.72 \pm 4.4	18.55 \pm 4.14	1.06	0.89
3.00	19.69 \pm 4.4	18.04 \pm 4.0	16.09 \pm 3.47	1.12	0.92
4.00	14.80 \pm 3.3	13.42 \pm 4.3	12.08 \pm 2.28	1.11	0.91
6.00	6.560 \pm 1.8	6.160 \pm 2.5	6.010 \pm 2.77	1.02	0.94
8.00	3.260 \pm 0.9	3.080 \pm 1.5	3.280 \pm 1.80	0.94	0.94
10.0	1.650 \pm 0.5	1.640 \pm 1.0	1.950 \pm 1.58	0.84	0.99
12.0	0.770 \pm 0.8	0.860 \pm 0.6	0.960 \pm 0.73	0.90	1.12

The mean ibuprofen profiles for the test and reference drug under non-fasting conditions appeared to be similar. The mean ibuprofen profile peaked at the same time (not T_{max}) for the test and reference drug products (1.5 hr, see the high-lighted values) under non-fasting condition. The ratio of mean test/reference was 0.98 at the time. For antipyresis 10 mcg/ml of plasma ibuprofen, is accepted as therapeutic level in febrile children. From above table it is evident that both drug products maintain that therapeutic ibuprofen levels from 0.5 to 4 hours (same as in the fasting study. See page 8). Thus, the ibuprofen plasma profiles obtained after two treatments under non-fasting condition appear to be satisfactory.

From the above table, the test, fasting, ibuprofen profile appears to be about 10% or more higher than the test non-fasting ibuprofen profile during 0 to 1.5 hours (see observation iv) after the Table 6).

The next step is to compare pharmacokinetic parameters of ibuprofen.

The test non-fasting AUC(0-T) values for subjects 1, 6 and 11, test fasting AUC(0-T) values for subjects 4, 7 and 13 and reference non-fasting AUC(0-T) values for subjects 2, 5 and 17 were calculated from their plasma ibuprofen profiles. These calculated values were

identical to the AUC(0-T) values reported by the firm. Thus, the spot checking showed the reliability of the firm's methods of calculating AUC(0-T) values. The firm has conducted ANOVA using term residuals (A and B) in the model. There was no significant residual effect in any pharmacokinetic parameter and their logtransforms. The table below shows the pharmacokinetic parameters of ibuprofen and their statistical analysis.

Table 6 : Mean and LS Mean Pharmacokinetic Parameters for Ibuprofen in a Single Dose (2x200mg), Non-fasting Study on 200mg/60mg Tablet

Parameter	Test Fast=A	Test Fed=B	Ref. Fed=C	Ratio (B/C)	Ratio (B/A)
Arithmetic Mean :					
Cmax (mcg/ml)	31.01 ±7.04	29.84 ±7.11	29.68 ±9.21	1.00	0.96
ln Cmax	3.408 ±0.24	3.371 ±0.23	3.345 ±0.31	1.03	0.96
LS Mean :					
Cmax (mcg/ml)	30.78	29.71	30.05	0.99	0.97
ln Cmax	3.401	3.361	3.363	1.00	0.96
Arithmetic Mean :					
AUC(0-T) mcgxhr/ml	118.10 ±19.09	104.10 ±17.59	101.60 ±19.44	1.03	0.88
ln AUC(0-T)	4.76 ±0.16	4.63 ±0.23	4.60 ±0.23	1.03	0.88
LS Mean :					
AUC(0-T) mcgxhr/ml	117.90	103.50	102.30	1.02	0.88
ln AUC(0-T)	4.76	4.63	4.61	1.02	0.88
Arithmetic Mean :					
AUC(0-inf) mcgxhr/ml	120.70 ±19.96	107.00 ±18.86	105.00 ±20.38	1.02	0.89
ln AUC(0-inf)	4.78 ±0.16	4.66 ±0.18	4.64 ±0.19	1.02	0.89
LS Mean :					
AUC(0-inf) mcgxhr/ml	120.60	106.60	105.50	1.01	0.88
ln AUC(0-inf)	4.78	4.66	4.64	1.02	0.89
Tmax hr	1.691 ±0.79	1.441 ±0.74	1.489 ±0.84	0.97	0.85
Half-life hr	1.957 ±0.18	2.026 ±0.30	2.150 ±0.53	0.94	1.04

The information in tables 5 and 6 showed that

- i) The test and reference non-fasting Cmax, AUC(0-T) and AUC(0-inf) values are bioequivalent by $\pm 20\%$ ratio criterion.
- ii) Mean, non-fasting, test Cmax (29.84 mcg/ml) and the peak value for non-fasting, test mean profile (24.3 mcg/ml - see table 5) are not close (ratio = 1.23). Similarly, the non-fasting, reference Cmax (29.68 mcg/ml) and the peak value for non-fasting, reference mean profile (24.85 mcg/ml - see table 5) are not close (ratio = 1.19).
- iii) Mean, non-fasting, test Tmax (1.441 hr) and the time to peak for the non-fasting test mean profile (1.5 hr - see table 5) are close (ratio = 0.96). Similarly, the mean, non-fasting, reference Tmax (1.489 hr) and time to peak for the non-fasting, reference mean profile (1.5 hr - see table 5) are close (ratio = 0.99)
- iv) Food did not appear to influence test Cmax and half-life values but may have reduced test AUC and Tmax values. This corroborates the information in drug labeling for Motrin^R (" When Motrin is administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption. The bioavailability of the drug is minimally altered by the presence of the food.")

The firm has also carried out ANOVA excluding the subject # 16. The Subject 16, had unusually high , level of ibuprofen at 8 hour. The repeat analysis, showed similar value which was pharmacokinetically anomalous. The firm, therefore, conducted the ANOVA with and without subject #16. Since there was no difference in the two ANOVAs and OGD generally does not allow exclusion of outlier, the ANOVA without subject 16 is not shown in this review.

Conclusion : Ibuprofen component of the test drug product is bioequivalent to the ibuprofen component of the reference drug product under non-fasting condition.

Pseudoephedrine HCl (PSE) :

Seventeen subjects completed the study. The firm stated as the LLOQ. Plasma profile of every subject was scanned and it was found that the firm has not reported any value below . The lowest value reported was for subject 7 at 24 hour when he received test drug product under non-fasting condition. The firm

did not provide any chromatograms for this subject. However it had provided a pertinent computer print out. The print out showed that subject # 7 who received test PSE, had chromatographic peaks ratio of _____ at 24 hour while the peaks ratio for lowest calibration std, _____ was _____. Similarly, from the computer print out for other chromatographic peaks ratios for the samples, reported as BLQ at time points other than 0.25 and 36 hours, were scrutinized. They were satisfactory. Some of these chromatograms were supplied. They were acceptable.

Individual plasma PSE profile is a very important parameter. It is an important supplementary information to compare every subject's test-PSE-profile to his reference-PSE-profile under non-fasting condition. The results are shown below.

Parameter	T > R	R > T	T = R	Descriptor
Pattern	-----	-----	-----	Same (17/17)
Cmax	-----	-----	-----	-----
Tmax	6/17	7/17	4/24	-----

Thus, following important items were evident in this comparison. i) All subjects have similar pattern of plasma profile. ii) The Cmax was evenly distributed iii) The Tmax was also evenly distributed. iv) Subject 10 showed delayed absorption (test and reference) of PSE (and not ibuprofen) under non-fasting condition.

Subsequent to this comparison, the mean test and reference plasma profiles were compared. The following table shows the comparison.

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ON ORIGINAL**

Table 7 : Mean Plasma Profile for PSE ng/ml \pm SD in a Single Dose (2x200mg/60mg), Non-fasting Study on 200mg/60mg Tablet

Time	A=Test (fast)	B=Test (fed)	C=Ref. (fed)	B/C	B/A
0	0	0	0	---	---
0.25	5.740 \pm 17.2	2.460 \pm 10	0.950 \pm 3.93	2.59	0.43
0.50	60.63 \pm 41.9	27.41 \pm 39	38.12 \pm 42.7	0.72	0.45
0.75	142.4 \pm 50.3	67.51 \pm 70	86.19 \pm 67.3	0.78	0.47
1.00	181.7 \pm 55.4	103.0 \pm 80	139.9 \pm 90.6	0.74	0.57
1.25	207.1 \pm 36.2	140.0 \pm 78	168.0 \pm 89.0	0.83	0.68
1.50	212.7 \pm 38.1	170.1 \pm 66	184.9 \pm 83.5	0.92	0.80
1.75	207.4 \pm 36.1	182.8 \pm 51	189.0 \pm 82.0	0.97	0.88
2.00	215.0\pm28.3	192.7 \pm 57	205.9 \pm 77.3	0.94	0.90
2.50	208.7 \pm 29.5	204.4\pm37	215.5\pm57.3	0.95	0.98
3.00	201.9 \pm 33.4	204.4 \pm 23	209.1 \pm 44.9	0.98	1.01
4.00	190.3 \pm 26.8	196.4 \pm 25	209.1 \pm 36.9	0.94	1.03
6.00	153.6 \pm 30.4	164.1 \pm 36	163.7 \pm 33.9	1.00	1.07
8.00	133.3 \pm 25.0	131.4 \pm 33	140.7 \pm 37.0	0.93	0.99
10.0	102.7 \pm 27.1	100.5 \pm 31	103.4 \pm 31.0	0.97	0.98
12.0	77.16 \pm 21.2	77.90 \pm 27	78.64 \pm 23.9	0.99	1.01
16.0	45.16 \pm 18.9	42.59 \pm 18	45.72 \pm 21.0	0.93	0.94
24.0	10.04 \pm 9.97	11.97 \pm 9	10.78 \pm 9.29	1.11	1.19
36.0	0.000 \pm 0.00	0.610 \pm 2	0.660 \pm 2.72	0.92	----

The mean PSE profiles for the test and reference drug appeared to be similar under non-fasting condition and almost identical from 1.5 hour to 36 hour. The mean reference PSE profile peaked at the same time (not Tmax) as the mean test profile (2.50 hr, see the high-lighted values). The ratio of mean test/reference was 0.95 at this time. Thus, according to this reviewer, the PSE plasma profiles obtained the test and reference treatments, under non-fasting condition, appear to be satisfactory. The food seem to delay the PSE absorption. The B/A ratio was lower from 0.25 hr to 2 hrs while from 2.5 hrs to 16 hrs it was around 1.

The next step is to compare pharmacokinetic parameters of PSE.

The test AUC(0-T) values for subjects 8, 11 and 13 and reference AUC(0-T) values for subjects 6, 7, 14 were calculated from their plasma PSE profiles. These calculated values were identical to the AUC(0-T) values reported by the firm. Thus, the spot checking showed the reliability of the firm's methods of calculating AUC(0-T) values. The table below shows the pharmacokinetic parameters of PSE and their statistical analysis.

Table 8 : Mean and LS Mean Pharmacokinetic Parameters for PSE in a Single Dose (2x200mg), Non-fasting Study on 200mg/60mg Tablet

Parameter	Test Fast = A	Test Fed = B	Ref. Fed = C	Ratio (B/C)	Ratio (B/A)
Arithmetic Mean :					
C _{max} (ng/ml)	235.4 ±34.9	233.3 ±24.3	244.7 ±35.3	0.95	0.99
ln C _{max}	5.451 ±0.24	5.447 ±0.23	5.491 ±0.31	0.96	1.00
LS Mean :					
C _{max} (ng/ml)	236.2	231.6	245.6	0.94	0.98
ln C _{max}	5.454	5.440	5.495	0.95	0.99
Arithmetic Mean :					
AUC(0-T) ngx _{hr} /ml	2142.4 ±423.3	2112.3 ±411.0	2196.7 ±496.5	0.96	0.99
ln AUC(0-T)	7.65 ±0.16	7.64 ±0.23	7.67 ±0.23	0.97	0.99
LS Mean :					
AUC(0-T) ngx _{hr} /ml	2151.5	2110.8	2189.1	0.96	0.98
ln AUC(0-T)	7.65	7.64	7.66	0.98	0.99
Arithmetic Mean :					
AUC(0-inf) ngx _{hr} /ml	2310.1 ±423.7	2236.1 ±424.4	2363.7 ±537.1	0.95	0.97
ln AUC(0-inf)	7.73 ±0.18	7.70 ±0.19	7.74 ±0.24	0.96	0.97
LS Mean :					
AUC(0-inf) ngx _{hr} /ml	2305.8	2249.0	2355.1	0.95	0.98
ln AUC(0-inf)	7.73	7.70	7.74	0.96	0.97
T _{max} hr	2.118 ±0.74	2.706 ±1.23	2.912 ±1.82	0.93	1.28
Half-life hr	4.962 ±0.80	4.911 ±1.00	5.039 ±1.59	0.99	0.99

The information in tables 7 and 8 showed that

- i) The test and reference non-fasting C_{max}, AUC(0-T) and AUC(0-inf) values are bioequivalent by ± 20% ratio criterion.

- ii) Mean, non-fasting, test Cmax (233.3 ng/ml) and the peak value for non-fasting, test mean profile (204.4 ng/ml - see table 7) are not similar (ratio = 1.14). Similarly, the non-fasting, reference Cmax (244.7 ng/ml) and the peak value for non-fasting, reference mean profile (215.5 ng/ml - see table 7) are not similar (ratio = 1.14).
- iii) Mean, non-fasting, test Tmax (2.706 hr) and the time to peak for the non-fasting test mean profile (2.5 hr - see table 7) are close (ratio = 1.08). While, the mean, non-fasting, reference Tmax (2.912 hr) and time to peak for the non-fasting, reference mean profile (2.5 hr - see table 5) are not close (ratio = 1.16)
- iv) Food did not appear to influence test Cmax, AUC and half-life values but may have increased test Tmax value.

Conclusion : PSE component of the test drug product is bioequivalent to the PSE component of the reference drug product under non-fasting condition.

THE BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITION IS ACCEPTABLE.

ADVERSE EVENTS :

Only two (dizziness and stomach burn) out of 7 reported events, were treatment related. These episodes occurred during trt A (test, fasting) and C (reference, non-fasting) respectively.

IN VITRO DISSOLUTION TESTING :

The dissolution procedure and data are shown at the end of the text. Those are acceptable.

RECOMMENDATIONS :

1. The fasting bioequivalence study conducted by Ohm Laboratories Inc. on its 200 mg/30 mg Ibuprofen/Pseudoephedrine HCl, Tablet, Lot # 13527, comparing it to Advil^R Cold and Sinus Tablet, 200 mg/30 mg, Tablet has been found acceptable by the Division of Bioequivalence.

2. The non-fasting bioequivalence study conducted by Ohm Laboratories Inc. on its 200 mg/30 mg Ibuprofen/Pseudoephedrine HCl, Tablet, Lot # 13527, comparing it to Advil^R Cold and Sinus Tablet, 200 mg/30 mg, Tablet has been found acceptable by the Division of Bioequivalence.
3. The studies demonstrate that Ohm laboratories' Ibuprofen/Pseudoephedrine HCl, 200 mg/30 mg Tablet is bioequivalent to the reference drug product, Advil^R Cold and Sinus Tablet manufactured by Whitehall Laboratories Inc., under fasting and non-fasting conditions.
4. The dissolution testing data are also acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability program. The dissolution testing should be carried out in 900 ml of Phosphate buffer at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification :

Not less than — of the labeled amount of drug (both components) in the dosage form is dissolved in 30 minutes.
5. From the Bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence study and in vitro dissolution testing. The ANDA 74-567 is, therefore, acceptable.

^
|S| 7/21/1995

S.G. Nerurkar, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED BY RPATNAIK
FT INITIALED BY RPATNAIK

Concur: 15/11 |S| Date: 7/21/95
 Keith K. Chan, Ph.D.
 Director, Division of Bioequivalence

cc: ANDA #74-567 original, HFD-630, HFD-604 (OGD, Hare), HFD-22 (Hooton), HFC-130(JAllen) HFD-655 (Patnaik, Nerurkar), Drug file

SGN/sgn/7-14-1995/A74567SD.094

Drug (Generic Name): Ibuprofen/Pseudoephedrine HCl

Firm: Ohm Labs. Inc.

Dose Strength: 200 mg/ 30 mg

ANDA # 74-567

Submission Date: October 31, 1994

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXIII Basket Paddle X RPM 50 No. Units Tested: 12

Medium: Phosphate Buffer pH 7.2 Volume: 900 ml

Reference Drug: (Manuf.) Advil^R Cold and Sinus

Assay Methodology: Not given

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) (Hr.)	Test Product			Reference Product		
	Lot #	Strength (mg)	Mean % Dissolved	Lot #	Strength (mg)	Mean % Dissolved
	<u>13527 biolot</u>	<u>200/30</u>		<u>H 225 biolot</u>	<u>200/30</u>	
		Range	(CV)		Range	(CV)

Sampling Times (Min.) (Hr.)	Lot # <u>13527 biolot</u>			Lot # <u>H225 biolot</u>		
	Strength (mg)	Mean % Dissolved	(CV)	Strength (mg)	Mean % Dissolved	(CV)
	<u>200/30</u>			<u>200/30</u>		

Specification: NLT in 30 mins (both components)

1) USP - Ibuprofen is racemate(S + R) and Pseudoephedrine HCl (PSE) is single dextrorotatory enantiomer

2) PDR - Pharmacokinetic (PK) information on ibuprofen is available but not on PSE. However, according to the "Orange Book" 29 ANDAs for ibuprofen, 200 mg tablet, have been approved to this date and PK information from those application will be more reliable.

Conclusion : based on the ANDAs on file, we need fasting and non-fasting study for ibuprofen. There is no need to measure metabolites of ibuprofen and measurement of enantiomer (S and R) is not essential.

4) Dr. Bradley's (Division of Biopharmaceutics) review of Sine-Aid IB from McNeil (NDA 19899). - A single dose (200mg/30mg), fasting, 4-treatment (test tablet, Nuprin tablet+ Sudafed tablet, Nuprin tablet and sudafed tablet), four period, 4-sequence study was carried out in 1989. The firm did not conduct food study.

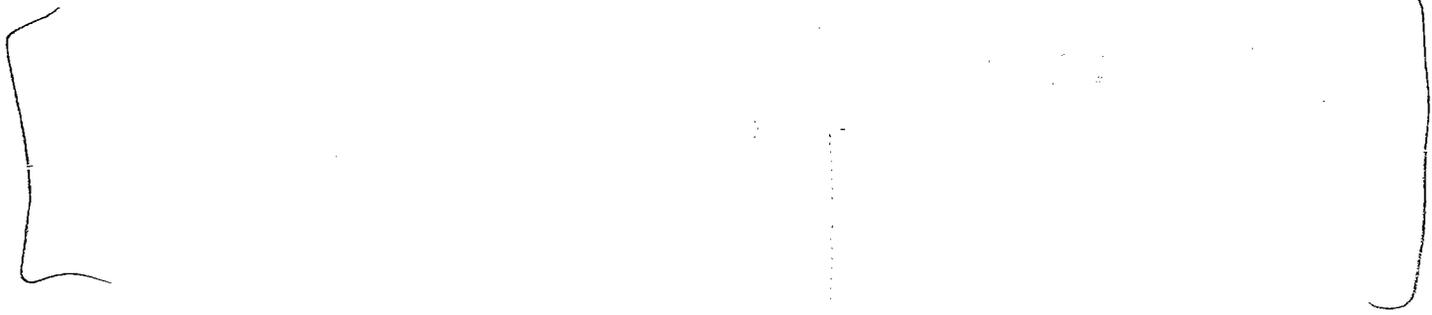
The firm also did not use available listed drug product (CoAdvil or Advil Cold and Sinus tablet)for the study. Instead, it used tablets for the individual active components of the combination drug product. The PK data for ibuprofen in this study, matches with the PK data on our files [AUC(0-T)=66.8, AUC(0-inf)= 68.6, Cmax= , Tmax=1.38 and Half-life=2.03]. This review was important to obtain PK data on pseudoephedrine (PSE) from an immediate release drug product. Those data are tabulated below.

Table 1 : PSE PK data from IR products

PKParameters	Test Tablet	Nuprin +Sudafed	Sudafed
Auc(0-T)	999.71	894.15	865.38
AUC(0-inf)	1203.2	1111.2	1124.5
Cmax	<u> </u>	<u> </u>	<u> </u>
Tmax	1.91	1.43	1.46
Half-life	6.79	6.8	7.02

Conclusion : Pseudoephedrine, a sympathomimetic drug indicated for nasal decongestion. The study did not measure active (6% metabolized to norpseudoephedrine) and inactive metabolite(s). According to its half-life, its advisable to collect blood samples upto 36 hours and not upto 24 hours.

4) **The Literature Search** - The Medline search yielded information about two ibuprofen metabolites (2-hydroxy and 2-carboxy) metabolites) pharmacokinetics and not about their efficacy. The information was available about two enantiomers (S and R) of ibuprofen. As per the OGD determination, it is not necessary to measure enantiomers for ibuprofen and the racemate measurement is sufficient. The Medline search for PSE did not yield any reference describing its metabolite norPSE during the years 1983 to 1995. Similarly, norPSE references were stand alone as a separate drug and did not show any connection with PSE.



**APPEARS THIS WAY
ON ORIGINAL**

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74.567

SPONSOR: OHM LABS INC

DRUG & DOSAGE FORM: IBUPROFEN / PSEUDOEPHEDRINE HCl TAB

STRENGTH/(s): 200 mg / 30 mg

TYPE OF STUDY: Single/Multiple Fasting/✓ Food ✓

STUDY SITE: _____

STUDY SUMMARY:	FASTING		NON FASTING		RATIO
	IBUPR	PSE	IBUPR	PSE	
C_{max}					0.95
AUC(0-∞)	1111/112 (97-104)	1983/1979 (96-107)	107/105 1.02	2236/2364	0.95
T_{max}	1.5/1.4	2.2/1.69	1.2/1.5 0.97	2.7/2.9	0.93
$T_{1/2}$	1.9/1.9	5.5/5.2	2/2.2 0.94	4.9/5.0	0.99

DISSOLUTION:

30 MIN
30 MIN

IBUPR

PSE

Q = NLT IN 30 MINS FOR BOTH

TEST REF.

PRIMARY REVIEWER:

BRANCH: 2

INITIAL: ISI

DATE: 7/21/1995

BRANCH CHIEF:

BRANCH: 2

INITIAL: ISI

DATE: 7/21/95

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: ISI

DATE: 9/12/95

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: ISI

DATE: 9/14/95

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-567

**ADMINISTRATIVE
DOCUMENTS**

3. For the 40 tablet size (round tablets and ~~tablets~~):
 - a. Relocate the statement, "See accompanying consumer...", and the storage statement so that they follow the DIRECTIONS section.
 - b. Increase the prominence of the statement, "See accompanying consumer...".

Unit Dose Blister:

1. Include the name of the manufacturer, city and state.
2. Include the strengths of the active ingredients if space permits.
3. For the round-shaped tablet, "tablet", rather than ~~tablets~~.
4. For the ~~tablets~~ tablet, "caplet", rather than ~~tablets~~.

Carton (unit dose, 10's and 20's and bottles, 40's; round tablets and ~~tablets~~):

See comments 1 and 2 for Container.

Insert (round tablets and ~~tablets~~):

At the bottom of your insert, include the name and place of business as described in 21 CFR 201.1. Also, include a revision date.

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their labels and labeling, then prepare and submit draft labeling.

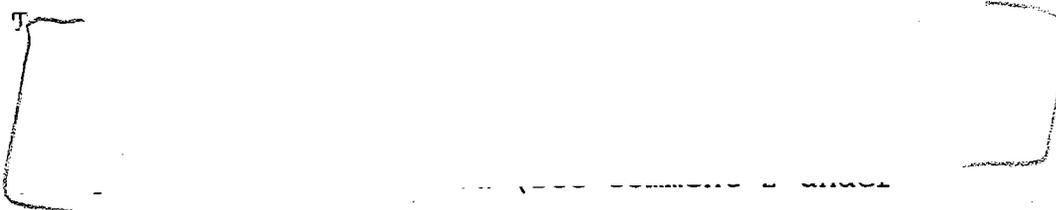
NOTE TO CHEMIST:

- 1.



2. The firm labels their product as having the following inactive ingredients: FD&C Blue #2 ~~_____~~, FD&C Red #40 ~~_____~~, FD&C Yellow #6 ~~_____~~; Iron Oxides, Lecithin, Pharmaceutical Glaze, Povidone, and Titanium Dioxide. Can these ingredients be found in ~~_____~~ listed as components?

FOR THE RECORD:

1. This product is a first generic. Patent expires November 12, 2002.
2. Review based on the latest approved labeling for NDA 19-771, Dimetapp Sinus®. This product is also marketed as Advil® Cold and Sinus. The applicant is being asked to revise labeling in accord with 21 CFR Parts 310, et. al. (Final Monograph for OTC Nasal Decongestant Drug Products; Final Rule) which takes effect on August 23, 1995. The final rule is for changes in the INDICATIONS and WARNINGS sections, including a drug interaction precaution for MAOI's.
3. 
4. Ohm plans to market this product as round tablets and ~~_____~~ tablets (caplets), in blister units of 10's and 20's, and in containers of 40's and 250 tablets with child-resistant closures. The 40 tablet container is to be cartoned and include a consumer labeling leaflet.
5. Storage:
ANDA: Store at room temperature; avoid excessive heat (40°C, 104°F).
NDA: Same as above.
6. Due to limited space on the container label, it was decided to allow "caplet" on the unit dose container label without the asterisked qualification that this is a capsule shaped tablet.
7. The proposed proprietary name, "Ibuprohm Cold and Sinus", was found to be acceptable by the CDER Labeling and Nomenclature Committee on 6/1/95.

ESTABLISHMENT EVALUATION REQUEST

OK 1/5/95

REQUEST TYPE (Check One) <input checked="" type="checkbox"/> Original <input type="checkbox"/> FollowUp <input type="checkbox"/> FUR	DATE July 5, 1995	PHONE NO. 301-594-0310	EER ID #
REQUESTORS NAME: John L. Smith	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-623
APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-567			
BRAND NAME: IBUPROHM Cold & Sinus Caplets	ESTABLISHED NAME: Ibuprofen and Pseudoephedrine Hydrochloride Tablets		
DOSAGE STRENGTH: 200 mg/30 mg			STERILE <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
PROFILE CLASS.: TCM	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)		
APPLICANT'S NAME: Ohm Laboratories, Inc.			
APPLICANT'S ADDRESS: P.O. Box 279 Franklin Park, NJ 08823			
COMMENTS : Firm wants to set the start of the expiration period as much as 60 days later for product in blister packages as for product in bottles. On the same subject, firm may use the term "date of release" to mean different things for blister-packed product and product in bottles, and the firm appears to define the date of manufacture as the END of the manufacturing process, not the start. Also, firm transports drug between two sites to do packaging in bottles and between cities to do packaging in blisters--we wonder if sufficient safeguards are used to protect product quality at these times. (This is page one of two.)			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

RESPONSIBILITY

DMF NUMBER/
PROFILE CODE

FKEY
CIRTS ID

HFD-324 USE
ONLY -

(Name and Complete Address)	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY -
1. Applicant 464-C Black Horse Lane S. Brunswick, NJ 08852	Primary manufacturing and testing facilities	tcm		
2. Applicant 1385 Livingston Ave N. Brunswick, NJ 08902	Alternate manufacturing and testing facilities	tcm		
3 [Handwritten]	[Handwritten]	ccs		
4 [Handwritten]	[Handwritten]	ccs		
[Handwritten]	[Handwritten]	nec		

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

QUEST TYPE (Check One) Original <input type="checkbox"/> FollowUp <input type="checkbox"/> FUR <input type="checkbox"/>		DATE July 5, 1995	PHONE NO. 301-594-0310	EER ID #
REQUESTORS NAME: John L. Smith		DIVISION: Office of Generic Drugs		MAIL CODE: HFD-623
APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-567				
BRAND NAME: IBUPROHM Cold & Sinus Caplets		ESTABLISHED NAME: Ibuprofen and Pseudoephedrine Hydrochloride Tablets		
DOSAGE STRENGTH: 200 mg/30 mg				STERILE <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
PROFILE CLASS:: TCM		PRIORITY CLASSIFICATION (See SMG CDER-4820.3)		
APPLICANT'S NAME: Ohm Laboratories, Inc.				
APPLICANT'S ADDRESS: P.O. Box 279 Franklin Park, NJ 08823				
COMMENTS : (see page one)				

(This is page two of two.)

FACILITIES TO BE EVALUATED

(Name and Complete Address)

RESPONSIBILITY

DMF NUMBER/
PROFILE CODE

FKEY
CIRTS ID

HFD-324 USE
ONLY

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY
1. [Redacted]	[Redacted]	nec		
2. [Redacted]	[Redacted]	nec		
3. [Redacted]	[Redacted]	nec		
4. [Redacted]	[Redacted]			
5. [Redacted]	[Redacted]			

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

RM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.

ANDA 74-567 HFD-623/Div File, HFD-617/JWilson, HFD-617/TAmes, HFD-623/JSimmone, HFD-623/GJSmith

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HFD-623

DATE: JUL 12 1995

TO: Director, Newark District, HFR-MA300

FROM: Chief,
Investigations & Compliance Evaluation Branch, HFD-324

SUBJ: Profile Class Not Previously Inspected
ANDA Inspection Request Applicant:
 ANDA 74-567, Ibuprofen Ohm Laboratories Inc.
 & Pseudoephedrine HCl Franklin Park, NJ 08823
 Tablets, 200 mg/30 mg

Establishment:
Ohm Laboratories
1385 Livingston Avenue
N. Brunswick, NJ 08902

PROFILE: TCM

REVIEWER: John Smith
TELEPHONE: 301-594-0310

CFN#: None

In connection with FDA's review of **ANDA 74-567**, please conduct a CGMP inspection of the referenced establishment. **The application provides for this establishment to be the alternate manufacturer and tester for the above listed drug product.** For guidance, refer to CP 7346.832, Pre-Approval Inspections.

In preparing this assignment, we relied on the MPQAS drug quality assurance profile which reports that the referenced establishment **has never been inspected for drug products** in the referenced profile class. If there has been recent coverage, or if the profile or location is not accurate, please call FTS 301-827-0062, within one week to discuss the need for the inspection and update the QAP through the usual means.

This application cannot be acted upon until the inspection is completed and your findings are reported to this office. Please call well in advance if you are unable to meet the time frame, whether due to priorities or the lack of readiness on the part of the firm.

Please send withhold and approval answers in the prescribed format via facsimile (FAX) 301-827-0145 or EMS as soon as possible after the completion of the inspection, before the report write up starts. If classified OAI, recommend withhold and provide complete establishment inspection report with exhibits documenting deficiencies to HFD-324 **within 30 days**. If NAI recommend approval via EMS and forward endorsement (FD-481(E)-CG) by mail.

In communicating with this office (FTS 301-827-0062), reference should be made to **ANDA 74-567**. Please direct your written response to the attention of the Investigations & Compliance Evaluation Branch, HFD-324.

for Mark A. Lynch *U*

Priority: ANDA Pending
Target Completion: **AUG 12 1995**

THIS REVIEW SUPERSEDES THE REVIEW DATED APRIL 21, 1995

REVIEW OF PROFESSIONAL LABELING #1
Original

DRAFT

DATE OF REVIEW: July 12, 1995

ANDA #: 74-567

NAME OF FIRM: Ohm Laboratories, Inc.

NAME OF DRUG: Ibuprofen and Pseudoephedrine Hydrochloride
Tablets, 200 mg/30 mg.

DATE OF SUBMISSION: January 24, 1995

COMMENTS:

General Comments:

1. The Agency recently published the final monograph for OTC nasal decongestant products. The monograph applies to combination products as well as single ingredient products. In it, the Agency modified labeling language in INDICATIONS and WARNINGS in §341.80. The final rule was published in the FEDERAL REGISTER on August 23, 1994. The effective date for the changes described in this final rule is August 23, 1995. Please make appropriate changes in your labeling.
2. Throughout your labeling for this product, define "caplet", as "capsule-shaped tablet", rather than

Container (40's and 250's-round tablets and tablets):

1. In accord with 21 CFR 201.61, the principle display panel of an over-the-counter drug in package form shall bear a statement of identity. The statement of identity shall be in terms of the established name of the drug followed by the pharmacological category. The pharmacological category of your product is "pain reliever/fever reducer/nasal decongestant". In addition, the statement of identity shall be presented in bold face type on the principle display panel in a size reasonably related to the most prominent printed matter. Please revise accordingly.

2. []

3. For the 40 tablet size (round tablets and ~~tablets~~):
 - a. Relocate the statement, "See accompanying consumer...", and the storage statement so that they follow the DIRECTIONS section.
 - b. Increase the prominence of the statement, "See accompanying consumer...".
4. The requirements of 21 CFR 201.1 (a) must be met.

Unit Dose Blister:

1. Include the name of the manufacturer, city and state.
2. Include the strengths of the active ingredients if space permits.
3. For the round-shaped tablet, "tablet", rather than "~~tablets~~".
4. For the ~~tablets~~ tablet, "caplet", rather than

Carton (unit dose, 10's and 20's and bottles, 40's; round tablets and ~~tablets~~):

See comments 1, 2 and 4 for Container.

Insert (round tablets and ~~tablets~~):

At the bottom of your insert, include the name and place of business as described in 21 CFR 201.1. Also, include a revision date.

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their labels and labeling, then prepare and submit draft labels and labeling.

NOTE TO CHEMIST:

- 1.



2. The firm labels their product as having the following inactive ingredients: FD&C Blue #2 _____, FD&C Red #40 _____, FD&C Yellow #6 _____, Iron Oxides, Lecithin, Pharmaceutical Glaze, Povidone, and Titanium Dioxide. Can these ingredients be found in _____ listed as components?

FOR THE RECORD:

1. This product is a first generic. Patent expires November 12, 2002.
2. Review based on the latest approved labeling for NDA 19-771, Dimetapp Sinus®. This product is also marketed as Advil® Cold and Sinus. The applicant is being asked to revise labeling in accord with 21 CFR Parts 310, et. al. (Final Monograph for OTC Nasal Decongestant Drug Products; Final Rule) which takes effect on August 23, 1995. The final rule is for changes in the INDICATIONS and WARNINGS sections, including a drug interaction precaution for MAOI's.
3. 
4. Ohm plans to market this product as round tablets and cablets (caplets), in blister units of 10's and 20's, and in containers of 40's and 250 tablets with child-resistant closures. The 40 tablet container is to be cartoned and include a consumer labeling leaflet.
5. Storage:
ANDA: Store at room temperature; avoid excessive heat (40°C, 104°F).
NDA: Same as above.
6. Due to limited space on the container label, it was decided to allow "caplet" on the unit dose container label without the asterisked qualification that this is a capsule shaped tablet.
7. The proposed proprietary name, "Ibuprohm Cold and Sinus", was found to be acceptable by the CDER Labeling and Nomenclature Committee on 6/1/95.

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secret and/or

confidential

commercial

information

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memo

&
2/23/95
email

10/13/95

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M E M O R A N D U M

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

DATE: June 9, 1995

FROM: William Russell, CSO, Regulatory Support Branch

SUBJ: Patent Certification

TO: ANDA 74-567 - Ohm Laboratories

A patent (4,552,899, exp 11/12/02) for Ibuprofen & Pseudoephedrine Tablets appeared in the 15th Edition of the Orange Book. I spoke to Arun Heble about this and he will submit a certification addressing his intentions regarding this patent.

**APPEARS THIS WAY
ON ORIGINAL**

name, but not in association with the established name. Revise the established name of your product to read -

Ibuprofen and Pseudoephedrine Tablets.

3. CONSUMER LABELING LEAFLET

See comment 2.b under container for _____ Tablets.

4. CARTON

a. Bottles of 40's Round- and _____ Tablets

See comment 2.b under container for _____ Tablets

b. Unit dose blister packages (1 x 10's & 1 x 20's)

See comment 2.b under container for _____ Tablets.

5. UNIT DOSE BLISTER

a. For the round-shaped tablet, "tablet", rather than " _____ [singular]

b. See comment 2.b under container for _____ Tablets.

Please revise your labels and/or labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison with your last submission with all differences annotated and explained.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	

Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
<i>PROPRIETARY NAME</i>			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? Yes If so, what were the recommendations? If the name was unacceptable, has the firm been notified?[See FTR]			
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
<i>LABELING</i>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	x		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.			x
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

[]

inactive ingredients. [See the tele-communication dated 7/23/96 in reference to the issue.]

FOR THE RECORD:

1. MODEL LABELING

The labeling of Advil Cold & Sinus Tablets (NDA 19-771/S-008, revised December 4, 1992, approved March 11, 1994).

2.



3.

4. This product is a first generic. Patent expires November 12, 2002. The firm amended its Patent Certification in the letter dated May 29, 1996. The firm challenged the expiration date of the Patent number 4,552,899 (NDA 19-771 Advil COLD & SINUS) and legal dispute on this patent is pending.

5. The firm was asked in the previous review to revise labeling in accord with 21 CFR Parts 310, et. al. (Final Monograph for OTC Nasal Decongestant Drug Products; Final Rule) which takes effect on August 23, 1995. The final rule is for changes in the INDICATIONS and WARNINGS sections, including a drug interaction precaution for MAOI's. We consider that this product is subject to the Monograph for OTC Nasal Decongestant Drug Products because this product contains pseudoephedrine. According to Susan Raigrodskis (CSO FOR Advil cold & Sinus) SLR-012 for NDA 19-771 was submitted on June 7, 1995 as a SSCBE to comply with the Final rule for Nasal Decongestants i.e. MAOI warning. This warning appears on the label currently being used for market sale.

6. Ohm plans to market this product as round tablets and tablets (caplets), in blister units of 10's and 20's, and in containers of 40's and 250 tablets with child-resistant closures. The 40 tablets container is to be cartoned and include a consumer labeling leaflet.

7. Storage:

be of actual size, color and clarity. Please assure that these are criteria met prior to submission of final print.

- e. We note that you have defined a caplet as an _____ . Please note that the term "caplet" is a contraction of capsule and tablet. Our office has been consistent in requesting that generic firms clarify "caplet" as a "capsule shaped tablet". Please reserve the term "caplet" for describing a "capsule shaped tablet" and clarify "caplet" as a "capsule shaped tablet" accordingly. We ask that you submit actual drawings of your drug product to disclose the shape of the tablet.

2. CONTAINER - 40's (Round-shaped & _____ Tablets)

a. 40's (Round-shaped & _____ Tablets)

- i. Revise the statement of identity including the established name and pharmacological category. The statement of identity should be in a size reasonably related to the most prominent printed matter on the principal display panel. We refer you to 21 CFR 201.61(c) for further guidance.
- ii. Increase the prominence of the term "Cold & Sinus" to make a clear distinction between this drug product and your Ibuprohm[®] product (ibuprofen only product).

b. 250's (Round-shaped & _____ Tablets)

- i. See comment (a)(i).
- ii. We encourage you to increase the prominence of the section heading "Drug Interaction Precaution" to be consistent with other section headings.

3. CARTON - 40's (Round-shaped & _____ Tablets)

See comments under CONTAINER (250's).

4. UNIT DOSE BLISTER LABEL: _____ Tablets

See GENERAL COMMENT (e).

5. UNIT DOSE CARTON LABELING: 1 x 10's and 1 x 20's
(Round-shaped & Tablets)

See comments under CONTAINER (250's).

6. CONSUMER LABELING LEAFLET

See comments under CONTAINER (250's).

Please revise your labels and labeling, as instructed above, and submit in final print, or in draft if you prefer.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

ISI
Jerry Phillips *oo* for / 7-23-97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES/QUESTIONS TO THE CHEMIST:

a.

[

]

b. Do you concur with the GENERAL comment (e)?

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
<i>PROPRIETARY NAME</i>			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? Yes If so, what were the recommendations? If the name was unacceptable, has the firm been notified?[See FTR]			
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	

Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			

12. Storage:

ANDA: Store at room temperature; avoid excessive heat (40°C, 104°F).

NDA: Same as above.

13. The proposed proprietary name, "Ibuprohm Cold and Sinus", was found to be acceptable by the CDER Labeling and Nomenclature Committee on 6/1/95.

Review cycle: #3 (FPL)

Primary Reviewer: Chan Park

Date: June 2, 1997

Secondary Reviewer: Charlie Hoppes

Date:

Team Leader: John Grace

Date:

cc:

ANDA 74-567
DUP/DIVISION FILE
HFD-613/CPark/CHoppes/JGrace (no cc)
njg/7/23/97/X:\NEW\FIRMSNZ\OHM\LTRS&REV\74567NA3.L
Review

APPEARS THIS WAY
ON ORIGINAL

CDER Establishment Evaluation Report
for July 02, 1997

Application: **ANDA 74567/000**
Stamp: **10-NOV-1994** Regulatory Due:
Applicant: **OHM**
279
FRANKLIN PARK, NJ 08823

Priority: _____ Org Code: **600**
Action Goal: _____ District Goal: **10-JAN-1996**
Brand Name: _____
Established Name: **IBUPROFEN;PSEUDOEPHEDRINE**
Generic Name: _____
Dosage Form: **TAB (TABLET)**
Strength: **200 MG/30 MG**

FDA Contacts:

Overall Recommendation:

Establishment: _____ DMF No: _____
_____ AADA No: _____

Profile: **CSN** OAI Status: **NONE** Responsibilities: _____
Last Milestone: **OC RECOMMENDAT 04-DEC-1996**
Decision: **ACCEPTABLE ✓**
Reason: **BASED ON PROFILE**

Establishment: _____ DMF No: _____
_____ AADA No: _____

Profile: **TCM** OAI Status: **NONE** Responsibilities: _____
Last Milestone: **OC RECOMMENDAT 04-DEC-1996**
Decision: **ACCEPTABLE ✓**
Reason: **BASED ON PROFILE**

Establishment: _____ DMF No: _____
_____ AADA No: _____

Profile: **CSN** OAI Status: **NONE** Responsibilities: _____
Last Milestone: **OC RECOMMENDAT 28-FEB-1997**
Decision: **ACCEPTABLE ✓**
Reason: **DISTRICT RECOMMENDATION**

Establishment: _____ DMF No: _____
_____ AADA No: _____

CDER Establishment Evaluation Report
for July 02, 1997

Profile: **NEC** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDAT 04-DEC-1996** **FINISHED DOSAGE RELEASE TESTER**
Decision: **ACCEPTABLE ✓**
Reason: **BASED ON PROFILE**

Establishment: **2244051** DMF No:
- **OHM LABORATORIES INC**
464-C BLACK HORSE LANE AADA No:
FRANKLIN PARK, NJ 08852

Profile: **TCM** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDAT 30-JAN-1997** **FINISHED DOSAGE MANUFACTURER**
Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRIC**

Establishment: **2248121** DMF No:
- **OHM LABORATORIES INC**
1385 LIVINGSTON AVE AADA No:
NORTH BRUNSWICK, NJ 08902

Profile: **NEC** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDAT 04-DEC-1996** **FINISHED DOSAGE MANUFACTURER**
Decision: **ACCEPTABLE ✓** **FINISHED DOSAGE RELEASE TESTER**
Reason: **BASED ON PROFILE**

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTI 03-APR-1997**

Establishment: _____ DMF No:
_____ AADA No:

Profile: **TCM** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDAT 04-DEC-1996** _____
Decision: **ACCEPTABLE ✓**
Reason: **BASED ON PROFILE**

Establishment: _____ DMF No: _____
_____ AADA No:

Profile: **CSN** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDAT 02-JUL-1997** _____

CDER Establishment Evaluation Report
for July 02, 1997

Page 3 of 3

Decision: **ACCEPTABLE** ✓
Reason: **DISTRICT RECOMMENDATION**

**APPEARS THIS WAY
ON ORIGINAL**

11/30/97
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commercial

information

be of actual size, color and clarity. Please assure that these are criteria met prior to submission of final print.

- e. We note that you have defined a caplet as an . Please note that the term "caplet" is a contraction of capsule and tablet. Our office has been consistent in requesting that generic firms clarify "caplet" as a "capsule shaped tablet". Please reserve the term "caplet" for describing a "capsule shaped tablet" and clarify "caplet" as a "capsule shaped tablet" accordingly. We ask that you submit actual drawings of your drug product to disclose the shape of the tablet.

2. CONTAINER - 40's (Round-shaped & Tablets)

a. 40's (Round-shaped & Tablets)

- i. Revise the statement of identity including the established name and pharmacological category. The statement of identity should be in a size reasonably related to the most prominent printed matter on the principal display panel. We refer you to 21 CFR 201.61(c) for further guidance.
- ii. Increase the prominence of the term "Cold & Sinus" to make a clear distinction between this drug product and your Ibuprohm[®] product (ibuprofen only product).

b. 250's (Round-shaped & Tablets)

- i. See comment (a) (i).
- ii. We encourage you to increase the prominence of the section heading "Drug Interaction Precaution" to be consistent with other section headings.

3. CARTON - 40's (Round-shaped & Tablets)

See comments under CONTAINER (250's).

4. UNIT DOSE BLISTER LABEL: Tablets

See GENERAL COMMENT (e).

5. UNIT DOSE CARTON LABELING: 1 x 10's and 1 x 20's
(Round-shaped & Tablets)

See comments under CONTAINER (250's).

6. CONSUMER LABELING LEAFLET

See comments under CONTAINER (250's).

Please revise your labels and labeling, as instructed above, and submit in final print, or in draft if you prefer.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

 ISI for /
Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

(FIRST GENERIC)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-567 Date of Submission: January 16, 1998

Applicant's Name: Ohm Laboratories, Inc.

Established Name: Ibuprofen 200 mg/Pseudoephedrine HCl 30 mg

Proprietary Name: Ibuprohm[®] Cold & Sinus Tablets

Labeling Deficiencies:

1. GENERAL COMMENTS:



2. CONTAINER - 40's (Capsule-shaped tablets)

Due to insufficient background contrast, in particular the black print on red background it is difficult to read the established name of your drug product. Please increase the readability by changing background and/or printing color. Please refer to 21 CFR 201.15(a)(6).

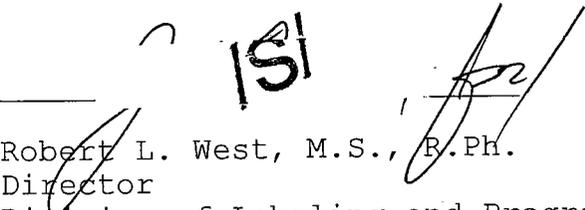
3. CARTON - 40's (Capsule-shaped tablets)

.See comment under CONTAINER and/or comment.

Please revise your labels and labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.


Robert L. West, M.S., B.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

(FIRST GENERIC)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-567 Date of Submission: January 16, 1998

Applicant's Name: Ohm Laboratories, Inc.

Established Name: Ibuprofen 200 mg/Pseudoephedrine HCl 30 mg

Proprietary Name: Ibuprohm® Cold & Sinus Tablets

Labeling Deficiencies:

1. GENERAL COMMENTS:

[

]

2. CONTAINER - 40's (Capsule-shaped tablets)

Due to insufficient background contrast, in particular the black print on red background it is difficult to read the established name of your drug product. Please increase the readability by changing background and/or printing color. Please refer to 21 CFR 201.15(a)(6).

3. CARTON - 40's (Capsule-shaped tablets)

See comment under CONTAINER and/or comment.

Please revise your labels and labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a

side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

ISI
Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

NOTES/QUESTIONS TO THE CHEMIST:



*The firm adequately addressed this issue
on p. 11 of this amendment. MMSust 7-22-98*

FOR THE RECORD:

1. MODEL LABELING

The labeling of Advil Cold & Sinus Tablets (NDA 19-771/S-008, revised December 4, 1992, approved March 11, 1994).

2. The reference listed drug has another approved name "Dristan Sinus". The supplement (19-771/S-002) for this additional name was submitted February 12, 1991 and approved April 8, 1997. This approved labeling was not used for side-by-side comparison.

3. Except container labels (40's - Caplet) and carton labeling (40's - Caplet), all labels and labeling is satisfactory in computer generated printer's proof as of 1/16/98 submission.

4. According to the FTR dated 2/10/93, the generic products will use "PAIN RELIEVER/FEVER REDUCER/NASAL DECONGESTANT" as the identity statement as dose the RLD Advil cold & Sinus. Other RLDS for this product, Dimetapp sinus and Dristan sinus have "PAIN RELIEVER/NASAL DECONGESTANT." as the pharmacologic category statement.

5. Regarding GENERAL COMMENTS in this review.



FORMULA" is an acceptable alternative. *Definition of "Modern"* is Webster's II - of relating to *advanced* style, technique, or technology.

6. One paragraph "Do not exceed ...occur." under WARNINGS has been relocated from the text and put into a different place from the innovator's labeling. We find this acceptable.
7. The text regarding MAOI in the "Drug Interaction Precaution" section is identical with the text appearing in the Federal Register (August 23, 1994), Final Monograph for OTC Nasal Decongestant Drug Products; Final Rule (21 CFR Parts 310, et al.).
8. The firm has defined a caplet as a "Capsule-Shaped Tablet" as requested by the Agency in the last labeling deficiency letter. The photo copy of the actual drug product (Caplet) appears to be a soft-gel capsule shape rather than conventional hard-gel capsule.
9. 
10. **This product is a first generic.** Patent expires November 12, 2002 according to the 17th edition "Orange Book" and 1st supplement. The firm's amended Patent Certification is accurate. The firm challenged the expiration date of the Patent number 4,552,899 (NDA 19-771 Advil COLD & SINUS) and legal dispute on this patent is pending.
11. The firm was asked in the previous review to revise labeling in accord with 21 CFR Parts 310, et. al. (Final Monograph for OTC Nasal Decongestant Drug Products; Final Rule) which takes effect on August 23, 1995. The final rule is for changes in the INDICATIONS and WARNINGS sections, including a drug interaction precaution for MAOI's. We consider that this product is subject to the Monograph for OTC Nasal Decongestant Drug Products because this product contains pseudoephedrine. According to Susan Raigrodskis (CSO FOR Advil cold & Sinus) SLR-012 for NDA 19-771 was submitted on June 7, 1995 as a SSCBE to comply with the Final rule for Nasal Decongestants i.e. MAOI warning. This warning appears on the current label being used for market sale. As of 5/10/97, this SLR-12 is approvable and the sponsor has to make further changes such as incorporation of Alcohol Warning. (Refer to the e-mail from Lissante LoBianco)
12. Ohm plans to market this product as and capsule-shaped tablets (caplets), in blister unit packages

of 10's and 20's, and in containers of 40's and 250 tablets with child-resistant closures. The 40 tablets container is to be cartoned and include a consumer labeling leaflet.

13. Storage:

ANDA: Store at room temperature; avoid excessive heat (40°C, 104°F).

NDA: Same as above.

14. The proposed proprietary name, "Ibuprohm Cold and Sinus", was found to be acceptable by the CDER Labeling and Nomenclature Committee on 6/1/95.

Review cycle: #4 (FPL)

Primary Reviewer: Chan Park

Date:

Team Leader: John Grace

Date:

ISI - 3/13/98

ISI

3/16/98

cc:

ANDA 74-567
DUP/DIVISION FILE
HFD-613/CPark/CHoppes/JGrace (no cc)
X:\NEW\FIRMSNZ\OHM\LTRS&REV\74567NA4.L
Review

RECORD OF TELEPHONE CONVERSATION

I initiated a phone call to Ms. Ternyik in reference to a labeling review that looks as if it was not sent with the chemistry comments back on September 28, 1998. I told her that there were a few labeling comments that needed to be adressed and I preceeded to fax a copy of these comments to her. She asked me if Ohm Labs could write a commitment letter stating that they would NOT market this product until the labeling changes requested were submitted to the Agency as a CBE supplement. I told her that I would check with my peers and I would get back to her on this proposition.

CC: ANDA 74-567
Div. File

DATE 5/4/99

ANDA NUMBER
74-567

IND NUMBER

TELECON

INITIATED BY Jim Barlow
MADE
APPLICANT/ BY
SPONSOR TELE.x

X FDA **IN**
PERSON

PRODUCT NAME
Ibuprofen &
Pseudophedrine
Tablets USP

FIRM NAME
Ohm Laboratories

**NAME AND TITLE OF
PERSON WITH WHOM
CONVERSATION WAS HELD**
Shirléy Ternyik
Associate
Director of
Regulatory
Affairs

TELEPHONE NUMBER
(609) 720-5612

SIGNATURE

TSI

CDER Establishment Evaluation Report
for September 22, 1998

Application: **ANDA 74567/000**
Stamp: **10-NOV-1994** Regulatory Due:
Applicant: **OHM**
279
FRANKLIN PARK, NJ 08823

Priority:
Action Goal:
Brand Name:
Established Name: **IBUPROFEN;PSEUDOEPHEDRINE
HYDROCHLORIDE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **200 MG/30 MG**

Org Code: 600

District Goal: 10-JAN-1996

FDA Contacts:

Overall Recommendation:

ACCEPTABLE on 20-APR-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: _____

DMF No: _____
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-DEC-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: _____

Establishment: _____

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-DEC-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: _____

Establishment: _____

DMF No: _____
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **28-FEB-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: _____

CDER Establishment Evaluation Report
for September 22, 1998

Establishment: _____

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-DEC-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: _____

Establishment: _____

DMF No: _____
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-JUL-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: _____

Establishment: **2244051**
OHM LABORATORIES INC
464-C BLACK HORSE LANE
FRANKLIN PARK, NJ 08852

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **20-APR-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE**
MANUFACTURER

Establishment: **2248121**
OHM LABORATORIES INC
1385 LIVINGSTON AVE
NORTH BRUNSWICK, NJ 08902

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-DEC-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE**
MANUFACTURER
FINISHED DOSAGE RELEASE
TESTER

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**

Department of Health and Human Services
 Public Health Service
 Food and Drug Administration
 ESTABLISHMENT EVALUATION REPORT
 for July 15, 1998

Requestor's Name: _____ **Division:** _____ **Phone:** _____

Application: ANDA 74567 **Brand Name:** _____
Established Name: IBUPROFEN;PSEUDOEPHEDRINE HYDROCHLORI
Strength: 200 MG/30 MG **Dosage Form:** TAB
Sponsor: OHM **Org Code:** 600 **Priority:** _____
Office: _____
Street: 279
City / State: FRANKLIN PARK, NJ 08823 **District Goal:** 10-JAN-96
Action Goal: _____ **User Fee Goal:** _____

Establishment: _____ **Name:** _____

Responsibilities	Dmf No	Profile	Status	Date
_____	_____	CSN	AC	04-DEC-96

Establishment: _____ **Name:** _____

Responsibilities	Dmf No	Profile	Status	Date
_____	_____	TCM	AC	04-DEC-96

Establishment: _____ **Name:** _____

Responsibilities	Dmf No	Profile	Status	Date
_____	_____	CSN	AC	28-FEB-97

Establishment: _____ **Name:** _____

Responsibilities	Dmf No	Profile	Status	Date
_____	_____	CTL	AC	04-DEC-96

Establishment: 2244051 **Name:** OHM LABORATORIES INC
 464-C BLACK HORSE LANE
 FRANKLIN PARK, NJ 08852

Responsibilities	Dmf No	Profile	Status	Date
FINISHED DOSAGE MANUFACTURER	_____	TCM	AC	20-APR-98

Department of Health and Human Services
 Public Health Service
 Food and Drug Administration
 ESTABLISHMENT EVALUATION REPORT
 for July 15, 1998

Requestor's Name:

Phone:

Application: ANDA 74567

Brand Name:

Established Name: IBUPROFEN;PSEUDOEPHEDRINE HYDROCHLORI

Sponsor: OHM

Strength: 200 MG/30 MG

Org Code: ~~603~~ **Priority:**

Office:

Street: 279

City / State: FRANKLIN PARK, NJ 08823

District Goal: 10-JAN-96

Action Goal:

User Fee Goal:

Establishment: 2248121

Name: OHM LABORATORIES INC
 1385 LIVINGSTON AVE
 NORTH BRUNSWICK, NJ 08902

Responsibilities	Dmf No	Profile	Status	Date
FINISHED DOSAGE MANUFACTURER		TCM	AC	20-APR-98
FINISHED DOSAGE RELEASE TESTER		CTL	AC	04-DEC-96

Establishment: _____ **Name:** _____

Responsibilities	Dmf No	Profile	Status	Date
_____		TCM	AC	04-DEC-96

Establishment: _____ **Name:** _____

Responsibilities	Dmf No	Profile	Status	Date
_____		CSN	AC	02-JUL-97

CSO	Date	Recommendation
DAMBROGIOJ	20-APR-98	ACCEPTABLE

September 18, 1997 Metro Park North II, Conference Room B
2-3:30 PM

Ohm Laboratories, Inc.

ANDA 74-567 Ibuprofen and Pseudoephedrine HCl Tablets, USP

Meeting Chair: Dr. Rashmikant Patel Sponsor Lead: Arun Heble

Introductions:

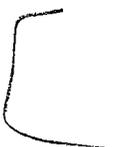
Arun R. Heble	Ohm Labs., Inc., President & C.O.O.
Joe Colaco	Ohm Labs., Inc., Vice President, Manufacturing
Dr. K.Ravi Reddy	Ohm Labs., Inc., Analytical Research
Dr. Temple Okarter	Consultant
Sanneke P.van Straten Murphy	Regulatory Compliance Consultant
James Sibert	Ranbaxy Pharmaceuticals Inc., Executive Director, Regulatory Affairs
Dr.Rashmikant Patel	FDA, Director, Div. Of Chemistry I OGD, CDER
Dr. Allen Rudman	FDA, Deputy Director, Div. Of Chemistry I OGD, CDER
Dr. Vilayat Sayeed	FDA, Team Leader, Branch I Chemistry Chemistry Division I, OGD, CDER
Dr. John Smith	FDA, Review Chemist, Branch I Chemistry Chemistry Division I, OGD, CDER
James Wilson	FDA, Project Manager, Branch I Chemistry Chemistry Division I, OGD, CDER

Meeting Objectives:

A meeting with Division representatives to discuss the OGD's deficiency letter of August 4, 1997 on ANDA 74-567 to assure Ohm that their third major response will answer all questions on the manufacture and control of this product.

Meeting Discussion Items:

Arun Heble	Introduction	5 minutes
■	Firm and product history	
Joe Colaco	<hr/>	10 minutes



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information

POST APPROVAL STABILITY COMMITMENTS AND PROTOCOL

Ibuprofen and Pseudoephedrine Tablets USP

Ohm Laboratories, Inc. commits itself to perform post-approval controlled room temperature stability studies (25°C - 30°C, ambient humidity) on the first three commercial production lots of tablets and caplets both, on the smallest and-largest container/closure system (bottles) and blister packaging. The attached protocol reflects this commitment.

In addition, to the first three commercial production lots, controlled room temperature studies (25°C - 30°C, ambient humidity) will be performed annually on one commercial production lot of tablets and caplets both, on the smallest and largest container/closure system (bottles), blister packaging and _____ Testing will be done at 0, 3, 6, 9, 12, 18, and 24 months.

Stability results for the drug product shall be reported in the annual report of the ANDA.

In addition, samples will be placed into the stability program at accelerated and controlled room temperature conditions when there is a significant change. Accelerated stability samples will be tested at 0, 1, 2 and 3 months.

Any production lot found to fall outside the approved specifications for the drug product will be investigated thoroughly and withdrawn from the market. However, if the investigation uncovers evidence that the deviation does not necessitate the removal of the drug product from distribution, OHM Laboratories shall immediately discuss the investigation results with the Agency and provide justification for the continued distribution of that production lot.

Any significant chemical, physical, or other deterioration which results in the distributed product acquiring non-compliant testing attributes will be reported to the FDA as a "Field Alert Report" [21 CFR314.81b)(1)(ii)].

3/5/99
TCM

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confidential

commercial

information

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: 5/4/99

To: OHM LABORATORIES

Phone: (609) 720-5612 Fax: (609) 720-1155

From: Jim Barlow (Landing) Fax 301-443-3847

Phone: (301) 827-5846 Fax: (301) 443-3847

Number of Pages: 3
(Including Cover Sheet)

Comments: _____

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(FIRST GENERIC)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-567 Date of Submission: January 16, 1998

Applicant's Name: Ohm Laboratories, Inc.

Established Name: Ibuprofen 200 mg/Pseudoephedrine HCl 30 mg

Proprietary Name: Ibuprohm[®] Cold & Sinus Tablets

Labeling Deficiencies:

1. GENERAL COMMENTS:

[

]

2. CONTAINER - 40's (Capsule-shaped tablets)

Due to insufficient background contrast, in particular the black print on red background it is difficult to read the established name of your drug product. Please increase the readability by changing background and/or printing color. Please refer to 21 CFR 201.15(a)(6).

3. CARTON - 40's (Capsule-shaped tablets)

See comment under CONTAINER and/or comment.

Please revise your labels and labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

|S|

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-567

APPLICANT: Ohm Laboratories, Inc.

DRUG PRODUCT: Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP

Labeling Deficiencies:

1. GENERAL COMMENTS:



We acknowledge the comment and Ranbaxy labeling will remain as is.

2. CONTAINER – 40'S (Capsule-shaped tablets)

Due to insufficient background contrast, in particular the black print on red background it is difficult to read the established name of your drug product. Please increase the readability by changing background and/or printing color. Please refer to 21 CFR 201.15(a) (6).

We commit to making the changes recommended in items 2 and 3, before commercialization and will submit changes as a "Changes Being Effected" supplement.

3. CARTON – 40's (Capsule-shaped tablets)

See comment under CONTAINER and/or comment.

See response under CONTAINER, item 2 and general comments.

(Approval Summary)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

3/8/01

ANDA Number: 74-567 Date of Submission: May 7, 1999 &
January 16, 1998
Applicant's Name: Ohm Laboratories, Inc.
Established Name: Ibuprofen 200 mg/Pseudoephedrine HCl 30 mg
Proprietary Name: Ibuprohm[®] Cold & Sinus Tablets

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels - 40's & 250's

Satisfactory in final print as of January 16, 1998
submission.

Carton Labeling - 40's

Satisfactory in final print as of January 16, 1998
submission.

Unit Dose Blister Label - 10's

Satisfactory in final print as of January 16, 1998
submission.

Unit Dose Carton Label - 10's & 20's

Satisfactory in final print as of January 16, 1998
submission.

Patient Information Leaflet -

Satisfactory in final print as of January 16, 1998
submission.

Revisions needed post-approval:

None (See "Other Comments" below.)

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Co-Advil Cold & Sinus Tablets

NDA Number: 19-771

NDA Drug Name: Co-Advil Cold & Sinus Tablets

NDA Firm: Ohm Laboratories

Date of Approval of NDA Insert and supplement #: 19-771/S-008
approved March 11, 1994, revised December 4, 1992.

Has this been verified by the MIS system for the NDA?

Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Most recently
approved labeling of the reference listed drug.

Basis of Approval for the Carton Labeling: Most recently approved
labeling of the reference listed drug.

Other Comments:

The Agency requested a **commitment letter NOT to market** this drug product until the changes requested by the Agency, faxed May 4, 1999, were made and submitted as a SSCBE. Once this SSCBE is submitted, the firm may market this product. (Note that this letter was received by the Agency May 7, 1999. Therefore, an approval summary has been drafted.)

FOR THE RECORD:

1. MODEL LABELING (All of the below are from previous review)

The labeling of CoAdvil Cold & Sinus Tablets (NDA 19-771/S-008, revised December 4, 1992, approved March 11, 1994).
2. The reference listed drug has another approved name "Dristan Sinus". The supplement (19-771/S-002) for this additional name was **submitted February 12, 1991 and approved April 8, 1997**. This approved labeling was not used for side-by-side comparison.
3. Except container labels (40's - Caplet) and carton labeling (40's - Caplet), all labels and labeling is satisfactory in computer generated printer's proof as of 1/16/98 submission.
4. According to the FTR dated 2/10/93, the generic products will use "**PAIN RELIEVER/FEVER REDUCER/NASAL DECONGESTANT**" as the identity statement as dose the RLD Advil cold & Sinus. Other RLDS for this product, Dimetapp sinus and Dristan sinus have "**PAIN RELIEVER/NASAL DECONGESTANT.**" as the pharmacologic category statement.

changes in the INDICATIONS and WARNINGS sections, including a drug interaction precaution for MAOI's. We consider that this product is subject to the Monograph for OTC Nasal Decongestant Drug Products because this product contains pseudoephedrine. According to Susan Raigrodkis (CSO FOR Advil cold & Sinus) SLR-012 for NDA 19-771 was submitted on June 7, 1995 as a SSCBE to comply with the Final rule for Nasal Decongestants i.e. MAOI warning. This warning appears on the current label being used for market sale. As of 5/10/97, this SLR-12 is approvable and the sponsor has to make further changes such as incorporation of Alcohol Warning. (Refer to the e-mail from Lissante LoBianco)

12. Ohm plans to market this product as round tablets and capsule-shaped tablets (caplets), in blister unit packages of 10's and 20's, and in containers of 40's and 250 tablets with child-resistant closures. The 40 tablets container is to be cartoned and include a consumer labeling leaflet.
13. Storage:
- ANDA: Store at room temperature; avoid excessive heat (40°C, 104°F).
- NDA: Same as above.
14. The proposed proprietary name, "Ibuprohm Cold and Sinus", was found to be acceptable by the CDER Labeling and Nomenclature Committee on 6/1/95.

Date of Review: 5/12/99

Date of Submission:

Primary Reviewer: Jim Barlow

Date: 5/17/99

Team Leader: John Grace

Date: 5/18/1999

cc:

ANDA: 74-567
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc,
V:\FIRMSNZ\OHM\LTRS&REV\74567ap.s
Review

4/9/99
T-com
3/1/01 T-com

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pages of trade

secret and/or

confidential

commercial

information

(Approval Summary)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-567 Date of Submission: March 28, 2001
Applicant's Name: Ohm Laboratories, Inc.
Established Name: Ibuprofen 200 mg/Pseudoephedrine HCl 30 mg
Proprietary Name: Ibuprohm[®] Cold & Sinus Tablets

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels – 40's & 250's

Satisfactory in **final print** as of March 28, 2001 submission.

Carton Labeling – 40's

Satisfactory in **final print** as of March 28, 2001 submission.

Unit Dose Blister Label – 10's

Satisfactory in **final print** as of March 28, 2001 submission.

Unit Dose Carton Label – 10's & 20's

Satisfactory in **final print** as of March 28, 2001 submission.

Patient Information Leaflet –

Satisfactory in **final print** as of March 28, 2001 submission.

Revisions needed post-approval:

Unit-Dose cartons for the coated CAPLETS; Back Panel;

Revise to read "**Ibuprohm Cold & Sinus**" [delete the _____] before "**Ibuprohm**"]

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Co-Advil Cold & Sinus Tablets

NDA Number: 19-771

NDA Drug Name: Co-Advil Cold & Sinus Tablets

NDA Firm: Ohm Laboratories

Date of Approval of NDA Insert and supplement #: 19-771/S-008 approved March 11, 1994, revised December 4, 1992.

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug.

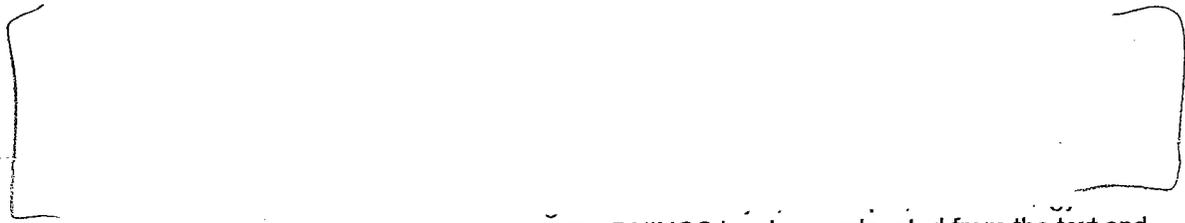
Basis of Approval for the Carton Labeling: Most recently approved labeling of the reference listed drug.

1. **Other Comments: Contacted Ms. S. Davis about deleting the _____ located before "Ibuprohm Cold & Sinus" on the back panel and told her to make the necessary revisions post approval. Also, note that new labeling for the reference listed drug was found to be APPROVABLE (Not approved) on March 28, 1997). Revisions may be requested in the not so distant future.**
2. **Note: That the proprietary name "Ibuprohm" was submitted to OPDRA on 3/9/01 & was found to be acceptable by OPDRA on 3/21/01**

FOR THE RECORD:

1. MODEL LABELING (All of the below are from previous review)
The labeling of CoAdvil Cold & Sinus Tablets (NDA 19-771/S-008, revised December 4, 1992, approved March 11, 1994).
2. The reference listed drug has another approved name "Dristan Sinus". The supplement (19-771/S-002) for this additional name was submitted February 12, 1991 and approved April 8, 1997. This approved labeling was not used for side-by-side comparison.
3. According to the FTR dated 2/10/93, the generic products will use "**PAIN RELIEVER/FEVER REDUCER/NASAL DECONGESTANT**" as the identity statement as does the RLD Advil cold & Sinus. Other RLDS for this product, Dimetapp sinus and Dristan sinus have "**PAIN RELIEVER/NASAL DECONGESTANT**" as the pharmacologic category statement.

4. Regarding GFNFRAL COMMENTS in previous review.



5. One paragraph "Do not exceed ...occur." under WARNINGS has been relocated from the text and put into a different place from the innovator's labeling. We find this acceptable.

6. The text regarding MAOI in the "Drug Interaction Precaution" section is identical with the text appearing in the Federal Register (August 23, 1994), Final Monograph for OTC Nasal Decongestant Drug Products; Final Rule (21 CFR Parts 310, et al.).

7. The firm has defined a caplet as a "Capsule-Shaped Tablet" as requested by the Agency in the last labeling deficiency letter. The photo copy of the actual drug product (Caplet)

8.



9. **This product is a first generic.** Patent expires November 12, 2002 according to the 17th edition "Orange Book" and 1st supplement. The firm's amended Patent Certification is accurate. The firm challenged the expiration date of the Patent number 4,552,899 (NDA 19-771 Advil COLD & SINUS) and legal dispute on this patent is pending.

10. The firm was asked in the previous review to revise labeling in accord with 21 CFR Parts 310, et. al. (Final Monograph for OTC Nasal Decongestant Drug Products; Final Rule) which takes effect on August 23, 1995. The final rule is for changes in the INDICATIONS and WARNINGS sections, including a drug interaction precaution for MAOI's. We consider that this product is subject to the Monograph for OTC Nasal Decongestant Drug Products because this product contains pseudoephedrine. According to Susan Raigrodskis (CSO FOR Advil cold & Sinus) SLR-012 for NDA 19-771 was submitted on June 7, 1995 as a SSCBE to comply with the Final rule for Nasal Decongestants i.e. MAOI warning. This warning appears on the current label being used for market sale. As of 5/10/97, this SLR-12 is approvable and the sponsor has to make further changes such as incorporation of Alcohol Warning. (Refer to the e-mail from Lissante LoBianco)

11. Ohm plans to market this product as round tablets and capsule-shaped tablets (caplets), in blister unit packages of 10's and 20's, and in containers of 40's and 250 tablets with child-resistant closures. The 40 tablets container is to be cartoned and include a consumer labeling leaflet.

12. Storage:

ANDA: Store at room temperature; avoid excessive heat (40°C, 104°F).

NDA: Same as above.

13. The proposed proprietary name, "Ibuprohm Cold and Sinus", was found to be acceptable by the CDER Labeling and Nomenclature Committee on 6/1/95 and again by OPDRA on March 21, 2001.

**APPEARS THIS WAY
ON ORIGINAL**

Date of Review: 3/30/01
Primary Reviewer: Jim Barlow

Date of Submission: 3/28/01

Date: 4/3/01

Team Leader: John Grace

Date: 4/3/2001

cc:

ANDA: 74-567
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSNZ\OHMLTRS&REV\74567AP.Sb
Review

RECORD OF TELEPHONE CONVERSATION

<p>Contacted Ms. Davis on 3/27/01 and let her know of several labeling revisions needed before full approval could be granted.</p> <ol style="list-style-type: none">1. Alcohol Warning revisions needed2. Color contrast/background revision <p>She informed me that she would begin working on this immediately.</p> <p>V:\FIRMSNZ\OHM\TELECONS\74567.32701</p> <p align="center">APPEARS THIS WAY ON ORIGINAL</p>	DATE 3/27/01
	APPLICATION NUMBERS 74-567
	IND NUMBER
	TELECON
	INITIATED BY __ APPLICANT / SPONSOR <input checked="" type="checkbox"/> FDA
	PRODUCT NAME Ibu[profen/pseudoephedrine
	FIRM NAME Ohm labs
	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Ms. Davis
	TELEPHONE NUMBER 609-720-5612
	SIGNATURE James Barlow

cc:
ANDA: 74-567
DUP/DIVISION FILE

Application Number Search Results from "OTC" table for query on "19771."

Appl No	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
019771	Yes	IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE	Tablet; Oral	200MG; 30MG	ADVIL COLD AND SINUS	WHITEHALL LABS

Thank you for searching the Electronic Orange Book

[Return to Electronic Orange Book Home Page](#)

APPEARS THIS WAY
ON ORIGINAL

Search results from the "OTC" table for query on "019771."

Active Ingredient:	IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	ADVIL COLD AND SINUS
Applicant:	WHITEHALL LABS
Strength:	200MG; 30MG
Application Number:	019771
Product Number:	001
Approval Date:	Sep 19, 1989
Reference Listed Drug:	Yes
RX/OTC/DISCN:	OTC
Patent and Exclusivity Info for this product:	Click Here

Thank you for searching the **Electronic Orange Book!**

[Return to Electronic Orange Book Home Page](#)

**APPEARS THIS WAY
ON ORIGINAL**

Patent and Exclusivity Search Results from query on 019771 001.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019771	001	4552899	APR 09,2004	
019771	001	4552899*PED	OCT 09,2004	

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

[Patent and Exclusivity Terms](#)

[Return to Electronic Orange Book Home Page](#)

APPEARS THIS WAY
ON ORIGINAL

Pediatric Exclusivity

There were no submissions for Pediatric Exclusivity that match the criteria specified.

**APPEARS THIS WAY
ON ORIGINAL**

Pediatric Rule

[Return to Pediatric Summary Search](#)

There were no submissions for the Pediatric Rule that match the criteria specified.

**APPEARS THIS WAY
ON ORIGINAL**

*Verified
Approved
Request*

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 74567/000**
Stamp: **10-NOV-1994** Regulatory Due:
Applicant: **OHM**
279
FRANKLIN PARK, NJ 08823

Priority:
Action Goal:
District Goal: **10-JAN-1996**

Brand Name:
Established Name: **IBUPROFEN;PSEUDOEPHEDRINE
HYDROCHLORIDE**

Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **200 MG/30 MG**

FDA Contacts: **E. MCNEAL (HFD-623) 301-827-5848 , Project Manager**
D. CUMMINGS (HFD-623) 301-827-5848 , Review Chemist
A. MUELLER (HFD-623) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 08-MAR-2001 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 27-MAR-2000 by M. GARCIA (HFD-322) 301-594-0095
WITHHOLD on 30-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 20-APR-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: _____ DMF No: _____
AADA No: _____

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **25-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: _____

RES 4/11/01

Establishment: _____ DMF No: _____
AADA No: _____

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **15-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: _____

RES 4/11/01

Establishment: _____ DMF No: _____
AADA No: _____

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 25-MAR-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment: _____

DMF No: _____
AADA No: _____

*Package 4110701
- This is*

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 25-MAR-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: _____

Establishment: _____

DMF No: _____
AADA No: _____

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 25-MAR-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: _____

Establishment: 2244051
OHM LABORATORIES INC
464-C BLACK HORSE LANE
FRANKLIN PARK, NJ 08852

DMF No: _____
AADA No: _____

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 30-MAR-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE
MANUFACTURER

Establishment: 2248121
OHM LABORATORIES INC
1385 LIVINGSTON AVE
NORTH BRUNSWICK, NJ 08902

DMF No: _____
AADA No: _____

Profile: TCM OAI Status: NONE

Responsibilities: FINISHED DOSAGE

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date **30-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

MANUFACTURER
FINISHED DOSAGE RELEASE
TESTER

Establishment: _____

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **25-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: _____

**APPEARS THIS WAY
ON ORIGINAL**

Redacted _____

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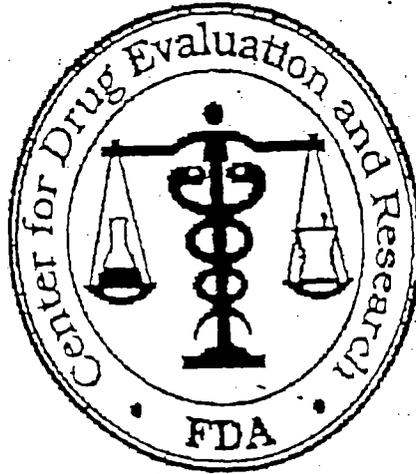
secret and/or

confidential

commercial

information

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS (HFD-600)
7500 STANDISH PLACE, ROCKVILLE, MD 20855



DATE: 4/18/01

TO: Shirley Terry, Jr

PHONE: 609-720-5812

FAX: 609-720-1155

FROM Tim Ames

PHONE: 301-827-5848

FAX: 301-594-0180

TOTAL NUMBER OF PAGES: 3
(EXCLUDING COVER SHEET)

SPECIAL INSTRUCTIONS:

Re: 74-567, Approval

Congratulations!

ISI

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION

ANDA APPROVAL SUMMARY

ANDA: 74-567

DRUG PRODUCT: Ibuprofen and Pseudoephedrine HCl Tablets USP

FIRM: Ohm Laboratories (A subsidiary of Ranbaxy Laboratories)

DOSAGE FORM: Tablets

STRENGTH(S): 200 mg/30 mg

CGMP STATEMENT/EER UPDATE STATUS: cGMP statement is satisfactory. EER acceptable (08-MAR-2001).

BIO STUDY: Satisfactory. The fasting and no-fasting bioequivalence studies conducted on Ibuprofen/Pseudoephedrine HCl Tablets were found to be acceptable (S.G. Nerurkar, 9/6/95)

METHOD VALIDATION - (Including dosage form description)
FDA method validation is not required. Both drug substance and drug product are compendial items.

STABILITY (Are containers used in the study same as the containers section?)

The containers used in the accelerated and room temperature stability studies are the same as proposed in the application.

Satisfactory accelerated ($40^{\circ}\text{C}\pm 2^{\circ}\text{C}$ at 75%±5% RH) and room temperature ($25^{\circ}\text{C}\pm 2^{\circ}\text{C}$ at 60%±5% RH) stability data are provided for the product packaged in 45 and 200 cc white bottles, and blister package. Data are within specs. A 24-month expiration is proposed by the firm.

LABELING REVIEW STATUS: Container, carton and package insert are satisfactory. (J. Barlow May 12, 1999)

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCHES - (FIRM'S SOURCE OF NDS O.K.):

For _____ (DMF # _____, Satisfactory)
For _____ (DMF # _____), Not Satisfactory due

to GMP issues, this is withdrawn)
For _____ (DMF # _____ Satisfactory)

Exhibit/Bio-batches

(Using _____ from _____
Lot 13527 _____ tablets

(Exhibit batch using _____
Lot 4239005 _____ tablets

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The size of bio-batch was _____ tablets which used _____

The size of exhibit batch was also _____ tablets which used _____ are essentially the same as those of the bio-batches.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?):

Proposed Production Batch Size = _____ tablets

The manufacturing processes are essentially the same as those of the bio-batches.

CHEMIST: RAJ BYKADI

March 2, 2001

cc: ANDA 74-567
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD 623/R. Bykadi/3/2/01
HFD-623/A.Mueller/3/2/01

Handwritten notes and stamps: "0 151", "H-4-01", "4-4-01", and a circular stamp.

4/9/01

Tcon

Redacted _____

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commercial

information

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-567

CORRESPONDENCE



NEW COPIES
NC

April 12, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS AND FAX

ADDITIONAL INFORMATION
PATENT-NOTICE OF DISMISSAL

**RE: Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP 200mg/30mg
ANDA 74-567
Patent- Notice of Dismissal**

Dear Sir/Madam:

Reference is made to the above pending ANDA 74-567 for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP 200mg/30mg. Reference is also made to the telephone call of April 12, 2001 requesting information pertaining to the Notice of Dismissal.

Further to our telephone call from this morning, regarding the referenced ANDA, we are enclosing herewith a copy of the Notice of Dismissal in Richardson-Vicks v. Ohm Laboratories, Inc., CV 96-3788; a copy of the letter from our attorney, Mr. Robert A. Dormer, to Mr. Gary Buehler in this regard and a copy of Mr. Buehler's response. Thus, Ohm Laboratories, Inc. has complied with 21 CFR § 314.95.

As we discussed, this dismissal does not constitute a "Court Decision" triggering generic 180 day exclusivity as contemplated in 21 U.S.C. § 355(j)(5)(B)(iv)(II). The triggering event would be the marketing of the product by a generic which obviously has not happened yet. Therefore, we believe Ohm Laboratories, Inc. is entitled to 180 day exclusivity assuming we are the first applicant to file an ANDA with a Paragraph IV certification.

If you have any questions or comments regarding this amendment, please call me at 609-720-5623 or Shirley TERNYK at 609-720-5612. Thank you.

Sincerely,

Stephanie J. Davis

Stephanie J. Davis
Manager Regulatory Affairs (for)
Shirley TERNYK
Official Agent for OHM Laboratories, Inc.



March 28, 2001

N/AF
ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX AND UPS OVERNIGHT

LABELING AMENDMENT

**RE: Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP,
 200mg/30mg
 ANDA 74-567**

Dear Sir/Madam:

Reference is made to the pending ANDA 74-567 for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP 200mg/30mg. Reference is also made to the telephone Labeling Deficiency received March 27, 2001.

The deficiency questions and corresponding responses are attached.

If you have any questions or comments regarding this amendment, please call me at 609-720-5623 or Shirley Terynik at 609-720-5612. Thank you.

Sincerely,

Stephanie Davis

Stephanie Davis
Manager Regulatory Affairs (for)
Shirley Terynik
Official Agent for Ohm Laboratories Inc.



pharmaceutical quality you can depend on

March 1, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS AND FAX

TELEPHONE AMENDMENT

ORIG AMENDMENT

N/AM

**RE: Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP,
200mg/30mg ANDA 74-567
Withdrawal Letter of _____**

Dear Sir/Madam:

Reference is made to the above pending ANDA 74-567 for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP, 200mg/30mg. Reference is also made to the telephone request of March 1, 2001 for an official Withdrawal Letter of: _____

Ohm Laboratories herewith withdraws _____

_____ as submitted in the February 7, 2000 Minor Deficiency response.

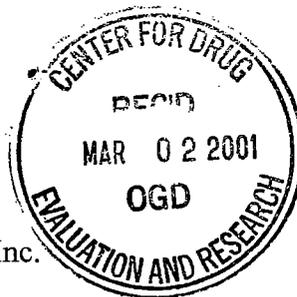
We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this amendment has been provided to the Food and Drug Administration, New Jersey District Office in Parsippany, New Jersey.

If you have any questions or comments regarding this amendment, please call me at 609-720-5623 or Shirley Ternyik at 609-720-5612. Thank you.

Sincerely,

Stephanie Davis

Stephanie J. Davis (for)
Shirley Ternyik
Official Agent for OHM Laboratories Inc.



pharmaceutical quality you can depend on



Am noted to cure Review for review 1st 2/6/01

January 30, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**FAX AND UPS OVERNIGHT
MINOR AMENDMENT**

MINOR AMENDMENT
Am

**RE: Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP,
200mg/30mg
ANDA 74-567**

Dear Sir/Madam:

Reference is made to the pending ANDA 74-567 for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP, 200mg/30mg. Reference is also made to the Minor Amendment deficiency dated December 5, 2000.

The deficiency questions are attached and responded to in the same order as they appear on the minor amendment.

We certify that a true copy of the technical section as described in 21 CFR 314.94 (d)(5) of this amendment has been provided to the Food and Drug Administration, New Jersey District Office in Parsippany, New Jersey.

If you have any questions or comments regarding this amendment, please call me at 609-720-5623 or Shirley Terynik at 609-720-5612. Thank you.

Sincerely,

Stephanie Davis

Stephanie Davis
Manager Regulatory Affairs (for)
Shirley Terynik
Official Agent for Ohm Laboratories Inc.



NW 2-

pharmaceutical quality you can depend on



11/2/00
AM noted to
CMC Reviewer
for Review
[Signature]

October 26, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX AND UPS OVERNIGHT

MINOR AMENDMENT

ORIG AMENDMENT

N/AM

**RE: Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP,
200mg/30mg
ANDA 74-567**

Dear Sir/Madam:

Reference is made to the pending ANDA 74-567 for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP, 200mg/30mg. Reference is also made to the Minor Amendment deficiency dated September 21, 2000.

The deficiency questions are attached and responded to in the same order as they appear on the minor amendment.

We certify that a true copy of the technical section as described in 21 CFR 314.94 (d)(5) of this amendment has been provided to the Food and Drug Administration, New Jersey District Office in Parsippany, New Jersey.

If you have any questions or comments regarding this amendment, please call me at 609-720-5623 or Shirley Terynik at 609-720-5612. Thank you.

Sincerely,

Stephanie Davis

Stephanie Davis (for)
Shirley Terynik
Official Agent for Ohm Laboratories Inc.



MLW
11-1-00

pharmaceutical quality you can depend on



Whitehall-Robins
Five Giralda Farms
Madison, NJ 07940-0871
Telephone (973) 660-5500
Website address: <http://healthfront.com>

cc: CP
RH
RW

✓ Fax to: Dettelbach
Dickinson

July 28, 2000

NDA 19-771
Advil Cold & Sinus Tablets

General Correspondence: U.S. Patent No. 4,552,899

Mary Ann Holovac, R.Ph.
Division of Data Management and Services
Room 3012
Food and Drug Administration
12420 Parklawn Drive
Rockville, MD 20857

Dear Ms. Holovac:

Reference is made to your telephone call of July 11, 2000 during which a request was made for information pertaining to U.S. Patent No. 4,552,899 listed under NDA 19-771 (Advil Cold and Sinus) in the Orange Book. In response to your inquiry please be advised as follows:

- 1) U.S. Patent No. 4,552,899 relates to combinations of NSAIDs and sympathomimetic amines. The patent was the subject of two reexamination proceedings in the U.S. Patent and Trademark Office. In its latest form, it contains thirty claims, numbered 21-50.
- 2) Certain of the patent's claims were asserted by its assignee, Richardson-Vicks, in a 1993 lawsuit against The Upjohn Co., McNeil PPC Inc. and Johnson & Johnson. Specifically, claims 36, 37, 47 and 48 were involved in the litigation. These claims involve mixtures of ibuprofen and pseudoephedrine in certain ratios. The majority of the non-asserted claims also relate to combinations of these two ingredients and cover the product of NDA 19-779.

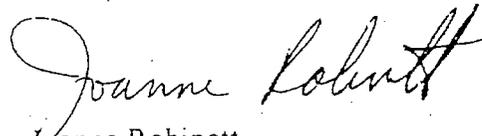
Whitehall-Robins Healthcare
General Correspondence: U.S. Patent No. 4,552,899
July 28, 2000

Page 2 of 2
Advil Cold & Sinus Tablets

- 3) At trial, the jury found the four claims in controversy to be valid and infringed. The jury's verdict, however, was subsequently overturned by the trial court judge who ruled that claims 36, 37, 47, and 48 of the patent were invalid due to obviousness. An appellate court sustained this holding of invalidity in a September, 1997 decision.
- 4) Despite the appellate court's ruling, it should be noted that none of the remaining claims in U.S. Patent No. 4,552,899 were involved in the lawsuit. Therefore, the entire patent has not been held invalid. The surviving twenty-six claims are due to expire on April 9, 2004.

If you have any questions regarding this matter, please don't hesitate to call me at 973-660-6167.

Sincerely yours,



Joanne Robinett
Director
Regulatory Affairs - Worldwide



June 13, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FEDERAL EXPRESS

ADDITIONAL INFORMATION
FOR PENDING AMENDMENT

RE: **Ibuprofen and Pseudoephedrine Hydrochloride
Tablets USP, 200mg/30mg
ANDA 74-567**

NDA ORIG AMENDMENT

N/Ac

Dear Sir/Madam:

Reference is made to the pending ANDA 74-567 for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP, 200mg/30mg. Reference is also made to the Amendment submission of February 7, 2000 (refer to **Attachment-1**).

To further support the Amendment submission of February 7, 2000, 3 months stability data is provided for the executed batch 4239005 (refer to **Attachment-2**).

If you have any questions or concerns regarding this correspondence, please call me at 609-720-5623 or contact Shirley TERNYIK at 609-720-5612. Thank you.

Sincerely,

Stephanie J. Davis (for)
Shirley TERNYIK
Official Agent for Ohm Laboratories, Inc.



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NEW CORRESP

MC

May 16, 2000

Mr. Nasser Mahmud
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FEDERAL EXPRESS AND FAX

CONTROLLED CORRESPONDENCE

RE: ANDA 74-567
Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP, 200mg/30mg
Request for a Copy of Previously Submitted Information

Dear Mr. Mahmud,

Reference is made to the pending ANDA 74-567 for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP, 200mg/30mg. Reference is also made to the telephone conversation with Shirley Ternyik during April, 2000 pertaining to obtaining a complete copy of the May 29, 1996 amendment of which Ohm does not have a copy.

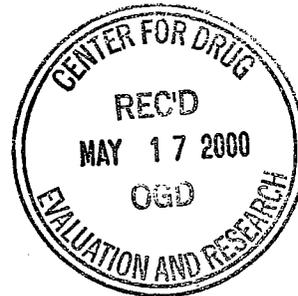
We request a complete copy of the May 29, 1996 amendment that was submitted by Ohm Laboratories, Inc. for the above referenced pending ANDA which changes Ohm's Paragraph III certification to a Paragraph IV certification.

If there are any questions or concerns, please call me at 609-720-5623 or Shirley Ternyik at 609-720-5612. Thank you.

Sincerely,

Stephanie J. Davis

Stephanie J. Davis (for)
Shirley Ternyik
Agent for Ohm Laboratories, Inc.



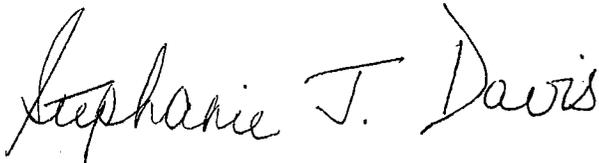
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*Stephanie
5-18-00*

Ibuprofen and Pseudoephedrine Hydrochloride Tablets, USP
ANDA 74-567
ADDITIONAL INFORMATION
FOR PENDING AMENDMENT
Page 2

If you have any questions or comments regarding this correspondence, please call me at 609-720-5623 or contact Shirley Ternyik at 609-720-5612. Thank you.

Sincerely,

A handwritten signature in cursive script that reads "Stephanie J. Davis". The signature is written in black ink and is positioned above the typed name and title.

Stephanie J. Davis (for)
Shirley Ternyik
Official Agent for Ohm Laboratories, Inc.

VE
1/14/00
NDA ORIG AMENDMENT
N/AC

February 7, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FEDERAL EXPRESS
MINOR AMENDMENT
REQUEST FOR EXPEDITED REVIEW

**RE: Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP,
200 mg/30 mg
ANDA 74-567**

Sponsor called 2/25/00
to ask if this would be considered
a minor amendment & if it could
be reviewed as expedited review.
Left voice message stating that
no expedited review is allowed on
non-approved applications
and a new
one will
be reviewed
as a
major
1/14/00
2/25/00

Dear Sir/Madam:

Reference is made to the above pending ANDA 74-567 for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP, 200 mg/30 mg. Reference is also made to the Minor Amendment deficiency received on June 17, 1999, re: to the _____ that was submitted in the original application. Reference is also made to the OGD policy dated July 26, 1996 titled "Substitution of _____ and _____ to MAPP 5240.1 titled "Requests for Expedited Review of Supplements to Approved ANDA's and AADA's". (See Attachment VIII).

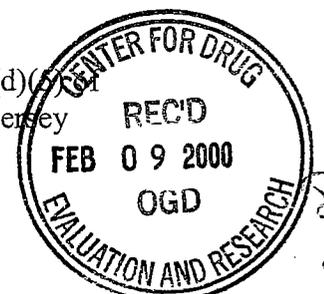
During recent conversations with _____, it was elucidated that the _____ facility (now called _____ where this _____ of time.

and Request Expedited Review.

An executed batch has been manufactured and the resulting data to support this _____ for review. This batch has been placed on stability and will be tested per the required intervals as in the original ANDA submission.

Also, _____ for the drug product have been _____

We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) for this amendment has been provided to the Food and Drug Administration, New Jersey District Office in Parsippany, New Jersey.



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02-600
MN

Office of Generic Drugs
ANDA 74-567
Minor Amendment
Request for Expedited Review
Page 2

If you have any questions or comments regarding this amendment, please call me at 609-720-5623 or Shirley Ternyik at 609-720-5612. Thank you.

Sincerely,

A handwritten signature in cursive script that reads "Stephanie J. Davis". The signature is written in black ink and is positioned above the typed name and title.

Stephanie J. Davis (for)
Shirley Ternyik
Official Agent for OHM Laboratories Inc.

ANDA DRUG AMENDMENT
N/A M

May 20, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX and FEDERAL EXPRESS

TELEPHONE AMENDMENT

**Re: Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP
ANDA 74-567**

Dear Sir/Madam:

Reference is made to our pending Abbreviated New Drug Application for Ibuprofen and Pseudoephedrine Tablets USP, ANDA 74-567.

Reference is also made to the FDA telephone call today with reference to two further items needed to complete the ANDA review.

We commit to changing the _____ test parameter for RSD from _____

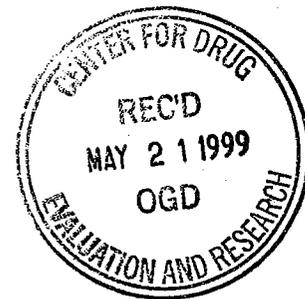
We are already using _____ as requested.

We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this amendment has been provided to the Food and Drug Administration, New Jersey District Office in Parsippany, New Jersey.

If you have any questions regarding this telephone amendment, please call me at (609) 720-5612. Thank you.

Sincerely,

Shirley Ternyik
Shirley Ternyik
Director Regulatory Affairs
Ranbaxy Pharmaceuticals, Inc.



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RANBAXY
PHARMACEUTICALS INC.

May 7, 1999

NEW CORRESP

NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**FAX and
FEDERAL EXPRESS**

**LABELING
FAX AMENDMENT**

**Re: Ibuprofen 200 mg and
Pseudoephedrine Hydrochloride Tablets 30 mg, USP
ANDA 74-567**

Dear Madam/Sir:

Reference is made to our pending Abbreviated New Drug Application for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP, ANDA 74-567.

Reference is also made to the FDA labeling fax amendment letter dated May 4, 1999. The questions and responses follow in the same order as in the letter. They are attached.

If you have any questions, regarding the amendment, please call me at (609) 720-5617.

Sincerely,

Pat Strasser (for)
Pat Strasser (for)
Shirley Temyik
Director Regulatory Affairs

RECEIVED

MAY 10 1999

GENERIC DRUGS

April 16, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT
jm
FAX and FEDERAL EXPRESS

TELEPHONE AMENDMENT

**Re: Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP
ANDA 74-567**

Dear Madam/Sir:

Reference is made to our pending Abbreviated New Drug Application for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP, ANDA 74-567.

Reference is also made to the telephone conversation of April 14, 1999 in regards to two further items needed to complete the ANDA review.

1. The functions of all of the components of the drug product are given in Attachment 1. The functions of the components of the _____ had been given earlier in the February 13, 1997 Major Amendment on page 156. It is also enclosed in Attachment 1. We have now added the functions for the components in the _____

2. We also commit to testing for _____ in the release of the finished drug product, on the first three commercial batches and then one batch annually thereafter. The specification will be NMT _____. The testing will be done by the same New Jersey Laboratories which performed the testing on the other batches.

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this amendment has been provided to the Food and Drug Administration New Jersey District Office in Parsippany, New Jersey.

If you have any questions, regarding the telephone amendment, please call me at (609) 720-5612.

Sincerely,

Shirley Ternyik
Shirley Ternyik

Director Regulatory Affairs
Ranbaxy Pharmaceuticals Inc.

RECEIVED

APR 19 1999

GENERIC DRUGS

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March 12, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX and FEDERAL EXPRESS

TELEPHONE AMENDMENT

NDA ORIG AMENDMENT

**Re: Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP
ANDA 74-567**

N/AM

Dear Madam/Sir:

Reference is made to our pending Abbreviated New Drug Application for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP, ANDA 74-567.

Reference is also made to the telephone conversation of March 5, 1999 in regards to our response dated November 23, 1998 of the FDA Minor Chemistry Deficiency Letter dated September 28, 1998.

As requested per the telephone conversation, responses 1 and 3 of the minor deficiency letter regarding the _____ are not appropriate to our application and are withdrawn.

Attached is a letter from _____ regarding the _____

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this amendment has been provided to the Food and Drug Administration New Jersey District Office in Parsippany, New Jersey.

If you have any questions, regarding the telephone amendment, please call me at (609) 720-5612.

Sincerely,

Pat Strasser
Pat Strasser (for)
Shirley Ternyik
Director Regulatory Affairs
Ranbaxy Pharmaceuticals Inc.

RECEIVED

MAR 15 1999

GENERIC DRUGS

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12/29/98
for

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commercial

information

November 23, 1998

ORIG AMENDMENT
N/AM

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX and
FEDERAL EXPRESS

MINOR AMENDMENT

**Re: Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP
ANDA 74-567**

Dear Madam/Sir:

Reference is made to our pending Abbreviated New Drug Application for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP, ANDA 74-567.

Reference is also made to the FDA Minor Chemistry Deficiency Letter dated September 28, 1998. The questions and responses follow in the same order as in the letter. They are attached.

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this amendment has been provided to the Food and Drug Administration New Jersey District Office in Parsippany, New Jersey.

If you have any questions, regarding the amendment, please call me at (609) 720-5612.

Sincerely,

Shirley Ternyik

Shirley Ternyik
Associate Director Regulatory Affairs
Ranbaxy Pharmaceuticals Inc.

RECEIVED

NOV 30 1998

GENERIC DRUGS

Shirley Ternyik
12/2/98

pharmaceutical quality you can depend on

January 16, 1998

ORIG AMENDMENT
N/A

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

MAJOR AMENDMENT

RE: IBUPROHM COLD AND SINUS TABLETS AND CAPLETS
(IBUPROFEN 200 mg/PSEUDOEPHEDRINE HCl 30 mg)
ANDA 74-567

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on October 31, 1994 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, for Ibuprofen and Pseudoephedrine Hydrochloride Tablets, 200 mg/30 mg, ANDA 74-567.

Reference is also made to our most recent amendment dated February 13, 1997, the subsequent chemistry and labeling (facsimile) deficiency letter dated August 4, 1997 and our meeting with OGD personnel on September 18, 1997.

Our response to the August 4, 1997 deficiency letter is as follows:

A. **Chemistry Deficiencies:**

1.



JAN 20 1998

GENERIC DRUGS

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Redacted _____

1/16/98
1 hr
in process

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NOTES
2/25/97
[Signature]

February 18, 1997

NEW CORRESP

NC

Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: IBUPROHM COLD AND SINUS CAPLETS AND TABLETS
(IBUPROFEN 200 mg/PSEUDOEPHEDRINE HCl 30 mg)
ANDA 74-567

Gentlemen:

Reference is made to our abbreviated new drug application submitted on October 31, 1994 pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act, for Ibuprofen and Pseudoephedrine Hydrochloride Tablets, 200 mg/30 mg.

Reference is also made to our most recent amendment dated February 13, 1997 in response to your November 20, 1996 (Chemistry) deficiency letter. On today's date we delivered a copy of our February 13, 1997 amendment to FDA's North Brunswick Resident Post. Copies of "Certification of Field Copy" including our cover letter to the North Brunswick Resident Post (dated February 18, 1997) are included herewith, for inclusion in our application.

Best Regards,

Sincerely,

[Signature]

Arun R. Heble
President & C.O.O

ARH/amb

RECEIVED
FEB 19 1997
GENERIC DRUGS

[Signature]
2-24-97

February 13, 1997



NDA ORIG AMENDMENT

Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

N/A

MAJOR AMENDMENT

RE: **IBUPROHM COLD AND SINUS CAPLETS AND TABLETS**
(IBUPROFEN 200 mg/PSEUDOEPHEDRINE HCl 30 mg)
ANDA 74-567

Gentlemen:

Reference is made to our abbreviated new drug application submitted on October 31, 1994 pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act, for Ibuprofen and Pseudoephedrine Hydrochloride Tablets, 200 mg/30 mg.

Reference is also made to your December 21, 1994 letter refusing to file our application, our subsequent major amendment dated January 24, 1995, your deficiency letter dated July 25, 1995, our subsequent major amendment dated April 30, 1996 and your most recent non-approvable letter dated November 20, 1996.

Our response to your most recent letter is as follows:

A. CHEMISTRY DEFICIENCIES:

QUESTION 1:

[]

RESPONSE:

In addition to the information previously submitted in our April 30, 1996 amendment (pages 028 and 029, section VII), we are submitting a reconciliation of the quantitative

[]

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confidential

commercial

information

In accordance with 21 CFR 314.94 (a)(8) (iv), we have provided a side-by-side comparison with our last submission, with all differences annotated and explained.

All information is included under SECTION V of our application.

Additional Question: Please commit to updating the tests and specifications for the drug substance and drug product per current USP requirements.

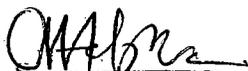
RESPONSE: For inclusion under SECTION VIII, please find updated "Methods and Specifications" dated 2/11/97 (Ibuprofen) and 2/11/97 (Pseudoephedrine Hydrochloride) for the drug substances. Updated "Methods and Specifications" (dated 2/11/97) for the drug products are submitted under SECTION XV. In this document we have changed the description of the products and we have added ~~.....~~ retention time as previously submitted.)

This concludes our response to your November 20, 1996 communication.

We appreciate your assistance during our December 16 telephone conference. Since this is a second MAJOR AMENDMENT, we anticipate that the administration will review the enclosed information most expeditiously.

We are anxiously awaiting the approval of this application.

Sincerely,



Arun R. Heble
President & C.O.O.

ARH/amb

1/8/97
1W

Redacted 2

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secret and/or

confidential

commercial

information

ANDA 74-567

Ohm Laboratories Inc.
Attention: Arun R. Heble
P.O. Box 279
Franklin Park, NJ 08823

NOV 20 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated October 31, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP, 200 mg/30 mg.

Reference is also made to your amendment dated April 30, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

1. Please reconcile the quantitative composition of the

[]

- 2 []

production batch. Please describe the test method and specifications.

3. The following comments pertain to the specifications for in-process

a. []

b. []

c. []

Redacted 2

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commercial

information

12.

B. Labeling Deficiencies:

1. GENERAL

[

]

2. CONTAINER

- a. 40's and 250's (Round-shaped Tablets)

Satisfactory in final print.

- b. 40's and 250's (Tablets)

The labeling of your product is not in accordance with 21 CFR 201.61. Since the term "caplet" is not an official USP dosage form classification, the established name of your product is Ibuprofen and Pseudoephedrine Tablets. The term "caplet" may be used as a part of your proposed proprietary name, but not in association with the established name. Revise the established name of your product to read -

Ibuprofen and Pseudoephedrine Tablets.

3. CONSUMER LABELING LEAFLET

See comment 2.b under container for Tablets.

4. CARTON

- a. Bottles of 40's Round- and Tablets

See comment 2.b under container for Tablets

- b. Unit dose blister packages (1 x 10's & 1 x 20's)

See comment 2.b under container for Tablets.

5. UNIT DOSE BLISTER

- a. For the round-shaped tablet, "tablet", rather than " [singular]
- b. See comment 2.b under container for: Tablets.

Please revise your labels and/or labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison with your last submission with all differences annotated and explained.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Please commit to updating the tests and specifications for the drug substance and drug product per current USP requirements.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

We note that this letter represents the second occasion on which significant (MAJOR) chemistry, manufacturing, and/or controls deficiencies have been identified which have precluded approval of your application. In an effort to facilitate the resolution of these deficiencies, we encourage you to contact Mr. James W. Wilson at 301-594-0310 for further clarification or assistance in providing a satisfactory response to each of the deficiencies.

Yours sincerely,

RS

11/19/96

cc Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

MORGAN & FINNEGAN, L.L.P.

A Registered Limited Liability Partnership

345 PARK AVENUE
NEW YORK, NEW YORK 10154-0053

TEL.: (212) 758-4800

TELEX 421792

FACSIMILE: (212) 751-6849

WASHINGTON OFFICE

1299 PENNSYLVANIA AVENUE, N.W.
SUITE 960

WASHINGTON, D. C. 20004

TEL.: (202) 857-7887

FACSIMILE: (202) 857-7929

WRITER'S DIRECT DIAL NUMBER:

(212) 415-8525

THOMAS M. HAMMOND*
SCOTT D. GREENBERG
MARK LEE HOGGE*
BRUCE D. DeRENZI
MARK J. ABATE
BARRY J. SCHINDLER
JOHN T. GALLAGHER
STEVEN F. MEYER
GABRIEL P. KRALIK
TONY V. PEZZANO
BRUCE D. RADIN
ANDREA L. WAYDA
ELAINE J. KAMAN
DESIREE M. STAHL
MARY J. MORRY
ROBERT K. GOETHALS
KENNETH H. SONNENFELD
JOHN W. OSBORNE
MICHAEL S. MARCUS*
RICHARD K. WARTHER
MICHAEL M. MURRAY*
CINDY M. ZELSON
LEIF R. SIGMOND, JR.*
LAURENCE J. BROMBERG
JEAN E. SHIMOTAKE†

M. CARAGH NOONE†
WALTER G. HANCHUK†
JEFFREY J. OELKE
OLIVER A. ZITZMANN
SCOTT B. HOWARD
PETER N. FILL
KENNETH S. WEITZMAN
RICHARD STRAUSSMAN
JAMES M. GIBSON
STEPHEN J. MANETTA
BRUNO POLITO
JAMES R. HASTINGS
BRENDA POMERANCE
CHRISTOPHER J. HAMATY*
KATHRYN E. DIAZ*
ALANA G. FIRESTER

SCIENTIFIC ADVISORS
KATHRYN M. BROWN, Ph.D.
LESLIE A. SERUNIAN, Ph.D.
DOROTHY R. AÜTH, Ph.D.
DAVID V. ROSSI, Ph.D.
CAROL GRUPPI, Ph.D.
RICHARD W. BORK, Ph.D.

*NOT ADMITTED IN NEW YORK FOREIGN LAW ADVISOR
†ADMITTED IN WASHINGTON, D.C. RYOSUKE FUJIMOTO

D. FOLEY
. DIAZ
J. P. DOWLING
C. VASSIL
WARREN H. ROTERT
ALFRED P. EWERT†
DAVID H. PFEFFER
HARRY C. MARCUS
ROBERT E. PAULSON
STEPHEN R. SMITH
KURT E. RICHTER
J. ROBERT DAILEY
EUGENE MOROZ
JOHN F. SWEENEY†
ARNOLD I. RADY†
CHRISTOPHER A. HUGHES

WILLIAM S. FEILER†
JANET DORE
JOSEPH A. CALVARUSO
JAMES W. GOULD†
RICHARD C. KOMSON
ISRAEL BLUM
CHRISTOPHER K. HU
BARTHOLOMEW VERDIRAME
DICKERSON M. DOWNING
MARIA C. H. LIN
JOSEPH A. DeGIROLAMO
CHRISTOPHER E. CHALSEN
MICHAEL A. NICODEMA
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SETH J. ATLAS
ANDREW M. RIDDLES

GEORGE B. FINNEGAN, JR.
JEROME G. LEE
ROGER S. SMITH
THOMAS I. O'BRIEN
RICHARD C. WITTE*
JOHN P. SINNOTT
NED W. BRANTHOVER
EUGENE C. RZUCIDLO*
COUNSEL

RESIDENT PARTNERS IN WASHINGTON
HARRY F. MANBECK, JR.*†
EDWARD A. PENNINGTON*†

JOHN D. MORGAN
1893-1939

HOBART N. DURHAM
1930-1969

GRANVILLE M. PINE
1939-1994

NEW CORRESP

NC

August 14, 1996

VIA FACSIMILE

CONFIRMATION VIA FEDERAL EXPRESS

United States Food And Drug Administration (301) 594-0183
Office Of Generic Drugs (HFD-6000)
Metro Park North
7520 Standish Place
Rockville, Maryland 20855

Re: ANDA Application No. 74-567

Dear Sirs:

We are patent counsel for Richardson-Vicks Inc. ("RVI").

In a letter dated June 28, 1996, RVI was notified that Ohm Laboratories, Inc. ("Ohm") located at 1385 Livingston Avenue, North Brunswick, New Jersey had filed an Abbreviated New Drug Application ("ANDA"). The ANDA was assigned Application No. 74-567. The established name of the proposed drug product which is the subject of Ohm's ANDA is ibuprofen 200 mg and pseudoephedrine hydrochloride 30 mg, and the name of the drug product is Advil Cold and Sinus; Tablet; Oral.

RECEIVED

AUG 15 1996

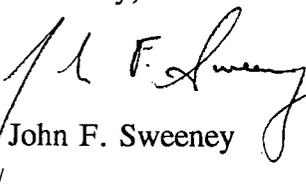
GENERIC DRUGS

United States Food And Drug Administration
Office Of Generic Drugs (HFD-600)
August 14, 1996
Page 2

RVI is the owner by assignment of original United States Patent No. 4,552,899 and reexamined U.S. Patent No. B1 4,552,899 entitled "Cough-Cold Mixtures Comprising Nonsteroidal Anti-Inflammatory Drugs" which is listed with respect to the proposed drug product on page AD28 of Approved Drug Products With Therapeutic Equivalence Evaluations (1996).

Pursuant to 21 C.F.R. § 314.107(f), notice is hereby provided to the FDA that on August 12, 1996, within forty-five days of receiving notice of Ohm's ANDA application, RVI filed a patent infringement action against Ohm in the United States District Court for the District of New Jersey pursuant to 35 U.S.C. § 271(e)(2)(A). A copy of the Complaint is attached. The action has been assigned Civil Action No. 96-3788 (WHW), and the case has been assigned to the Honorable William H. Walls.

Sincerely,


John F. Sweeney

JFS:bm

Enclosure

cc: Dr. Arun Heble, President, Ohm Laboratories, Inc.
Charles Guttman, Esq.
James S. Rubin, Esq.

Arnold B. Calmann (AC 3245)
David J. Satz (DS 4628)
SAIBER, SCHLESINGER, SATZ & GOLDSTEIN
One Gateway Center
Newark, New Jersey 07102
(201) 622-3333

OF COUNSEL

John F. Sweeney (JS 5431)
Richard C. Komson (RK 7245)
John T. Gallagher (JG 5744)
MORGAN & FINNEGAN, L.L.P.
345 Park Avenue
New York, New York 10154
(212) 758-4800

Attorneys for Plaintiff
RICHARDSON-VICKS, INC.

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

-----)	
RICHARDSON-VICKS INC.,)	
)	
Plaintiff,)	
)	
v.)	Civil Action No. 96-3788 (WHW)
)	
OHM LABORATORIES, INC.,)	COMPLAINT
)	
Defendant.)	
-----)	

Plaintiff, RICHARDSON-VICKS INC. ("RVI"), One Procter & Gamble Plaza, Cincinnati, Ohio 45202, for its Complaint against Defendant, OHM LABORATORIES, INC. ("OHM"), alleges, upon knowledge as to its own acts, and upon information and belief as to the acts of others, that:

JURISDICTION AND VENUE

1. This action arises under the United States Patent Laws, Title 35, United States Code. This Court has jurisdiction over the subject matter of this action pursuant to

28 U.S.C. §§ 1331 and 1338. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(c) and 1400(b).

PARTIES

2. Plaintiff RVI is a corporation organized under the laws of the State of Delaware and conducts business within this judicial district.

3. Upon information and belief, defendant OHM is a corporation organized under the laws of the State of New Jersey and has an office and principal place of business at 1385 Livingston Avenue, North Brunswick, New Jersey.

BACKGROUND

4. Plaintiff RVI is the owner by assignment of original United States Patent No. 4,552,899 (the "'899 patent") and Re-examination Certificate No. B1 4,552,899 (the B1 "'899 patent") for an invention entitled "Cough-Cold Mixtures Comprising Nonsteroidal Anti-Inflammatory Drugs". The '899 patent, which issued on November 12, 1985, was subjected to two re-examination proceedings in the United States Patent and Trademark Office. The re-examinations were consolidated and resulted in the issuance of the B1 '899 patent on October 20, 1992. A copy of the reexamined B1 '899 patent and original '899 patent is attached as Exhibit A.

5. The B1 '899 patent has thirty (30) claims, Claims 21-50. Claims 21-23, 25-26, 28, 31-37, 40-42 and 44-48 are directed to pharmaceutical compositions and methods of treatment with ibuprofen and pseudoephedrine as active ingredients and specifically to a composition containing 200 mg ibuprofen and 30 mg pseudoephedrine.

6. In September 1989, American Home Products Corp. ("AHP") received approval of its New Drug Application ("NDA") from the United States Food and Drug Administration ("FDA") to market a product containing 200 mg ibuprofen and 30 mg pseudoephedrine. AHP's product was initially marketed under the tradename Co-Advil. The name of the product was subsequently changed to Advil® Cold & Sinus.

7. In October 1992, in the United States District Court for the District of Delaware (Civil Action No. 92-634), RVI commenced a patent infringement action against AHP alleging that AHP's manufacture and sale of the Advil® Cold & Sinus ibuprofen/pseudoephedrine product infringed the B1 '899 patent.

8. The action was settled by the parties prior to trial. In the settlement, RVI granted AHP a sole license under the B1 '899 patent, and AHP granted RVI rights under its NDA.

9. On or about September 1993, The Upjohn Company ("Upjohn") commercially introduced a product having 200 mg ibuprofen and 30 mg pseudoephedrine under the tradename Motrin® IB Sinus.

10. On or about September 1993, McNeil-PPC and Johnson & Johnson (collectively "McNeil") commercially introduced a product having 200 mg ibuprofen and 30 mg pseudoephedrine under the tradename Sine-Aid® IB.

11. In July 1994, RVI began selling a product having 200 mg ibuprofen and 30 mg pseudoephedrine. That product is marketed under the tradename DayQuil® Sinus Pressure and Pain with Ibuprofen .

12. As of 1993, the ibuprofen/pseudoephedrine product covered by the B1 '899 patent had gained a strong market position and had established annual sales of approximately \$50 million.

13. In December 1993, in the United States District Court for the District of Delaware (Civil Action No. 93-556), RVI commenced a patent infringement action against Upjohn and McNeil alleging that the manufacture and sale of Upjohn's Motrin® IB Sinus ibuprofen/pseudoephedrine product and Upjohn's Sine-Aid® IB ibuprofen/pseudoephedrine product infringed Claims 36, 37, 47 and 48 of the B1 '899 patent.

14. The District Court ruled as a matter of law that Upjohn's Motrin® IB Sinus product and McNeil's Sine-Aid® IB product infringed Claims 36, 37, 47 and 48 of the B1 '899 patent.

15. Upjohn and McNeil contended that Claims 36, 37, 47 and 48 of the B1 '899 patent were not valid under 35 U.S.C. § 103 for obviousness and/or not valid under 35 U.S.C. § 102(g) because of an alleged prior invention by AHP.

16. After a twelve (12) day trial, the jury returned verdicts in favor of RVI that Upjohn and McNeil had failed to prove by clear and convincing evidence that Claims 36, 37, 47 and 48 of the B1 '899 patent were not valid under 35 U.S.C. § 103 and/or 35 U.S.C. § 102(g) and awarded RVI damages based on a reasonable royalty of 7% for Upjohn's and McNeil's infringing sales.

17. On May 10, 1995, the District Court entered judgment in favor of RVI based on the jury verdicts.

18. Subsequently, Upjohn and McNeil filed motions for judgment as a matter of law pursuant to Rule 50(b), Fed. R. Civ. P., requesting that the District Court, *inter alia*, enter a judgment that Claims 36, 37, 47 and 48 of the B1 '899 patent are not valid.

19. On January 17, 1996, eight months after the jury verdict and the original judgment, the District Court, without entertaining oral argument, granted judgment as a matter of law that Claims 36, 37, 47 and 48 of the B1 '899 patent are not valid for obviousness and for prior invention.

20. On February 6, 1996, RVI timely filed a Notice of Appeal to the United States Court of Appeals for the Federal Circuit. Upjohn and McNeil did not cross-appeal the District Court's judgment that their respective products infringe the B1 '899 patent.

21. On appeal, RVI demonstrated that in entering judgment as a matter of law that the B1 '899 is not valid, the District Court, *inter alia*, improperly substituted its own views for those of the jury, used the wrong legal standard in analyzing the alleged prior invention of AHP, and impermissibly selected evidence to buttress its own opinion while ignoring the substantial evidence which supports the jury verdicts. RVI's arguments to the Court of Appeals for the Federal Circuit demonstrate RVI's good faith belief that Claims 36, 37, 47 and 48 of the B1 '899 patent are valid and that the Court of Appeals will ultimately vacate the District Court's judgment of invalidity and reinstate the jury verdicts.

22. Briefing by the parties was completed in July 1996. The Joint Appendix was filed on August 1, 1996. The Court of Appeals should schedule oral

argument shortly and a decision could be expected within the next six months. In view of the appeal addressing the validity of certain claims of the B1 '899 patent, RVI is agreeable to staying this action pending the decision by the Court of Appeals for the Federal Circuit. Thus, RVI will file a motion to stay this action in the near future.

PROCEEDINGS BEFORE THE FDA

23. Pursuant to the Food, Drug and Cosmetic Act ("FDCA") [*i.e.*, 21 U.S.C. § 321 *et seq.*], the FDA is responsible for determining whether a generic drug product should be approved for sale.

24. Pursuant to Section 505(j) of the FDCA [*i.e.*, 21 U.S.C. § 355(j)], a pharmaceutical manufacturer seeking approval to market a generic version of a patented drug may submit an Abbreviated New Drug Application ("ANDA") to the FDA.

25. Section 505 (j)(2)(A)(vii)(I)-(IV) of the FDCA [*i.e.*, 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV)] requires that an applicant submitting an ANDA must certify one of four things: (1) that the drug for which the ANDA is submitted has not been patented ("paragraph I certification"); (2) that the patent on such drug has expired ("paragraph II certification"); (3) the date on which the patent on such drug will expire if it has not yet expired ("paragraph III certification"); or (4) that the patent on such drug is not valid or will not be infringed by the manufacture, use and/or sale of the drug for which the ANDA has been submitted ("paragraph IV certification"). The certification requirements of Section 505(j) of the FDCA are also set forth in 21 C.F.R. § 314.107(b)(1)(i)-(iv).

26. Section 505(j)(2)(B) of the FDCA [*i.e.*, 21 U.S.C. § 355(j)(2)(B)] requires that when an applicant submits an ANDA containing a paragraph IV certification,

the ANDA applicant must provide the owner of the relevant patent notice of the applicant's submission of the certification to the FDA.

27. Section 505(j)(4)(B)(iii) of the FDCA [*i.e.*, 21 U.S.C. § 355(j)(4)(B)(iii)] requires that if the ANDA contains a paragraph IV certification, and all applicable scientific and regulatory requirements have been met, the FDA's approval of the ANDA "shall be made effective immediately" unless the patent owner brings an action for infringement pursuant 35 U.S.C. § 271(e)(2)(A) within forty-five (45) days of receiving notice from the ANDA applicant that an ANDA has been submitted to the FDA. This provision of the FDCA is also set forth in 21 C.F.R. § 314.107(b)(3).

28. Pursuant to 35 U.S.C. § 271(e)(2)(A), "[i]t shall be an act of infringement to submit . . . an application under Section 505(j) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. § 355(j)] . . . for a drug claimed in a patent or the use of which is claimed in a patent . . . if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent."

29. Section 505(j)(4)(B)(iii)(I)-(III) [*i.e.*, 21 U.S.C. § 355(j)(4)(B)(iii)(I)-(III)] requires that once the patent owner commences an infringement action pursuant to 35 U.S.C. § 271(e)(2)(A), the FDA shall suspend approval of the ANDA until the earliest of three dates: (i) the date of the court's decision holding that the patent is not valid or not infringed; (ii) the date the patent expires if the court determines that the patent is infringed; or (iii) subject to modification by the court, thirty months from the patent owner's receipt of notice of the ANDA applicant's filing of a paragraph IV certification with the FDA.

30. Under 21 C.F.R. § 314.107(e), the court decision is one from which no appeal can be or has been taken.

COUNT FOR PATENT INFRINGEMENT

31. In a letter dated on June 28, 1996, defendant OHM notified plaintiff RVI of its submission of its paragraph IV certification to the FDA. RVI received OHM's letter on July 1, 1996.

32. Defendant OHM's letter dated June 28, 1996 states that OHM has submitted an ANDA to the FDA "in order to obtain approval to engage in the commercial manufacture, use or sale" of a product containing 200 mg ibuprofen and 30 mg pseudoephedrine prior to the expiration of the B1 '899 patent.

33. Based on its June 28, 1996 letter, Defendant OHM is prepared to manufacture and sell a product containing 200 mg ibuprofen and 30 mg pseudoephedrine and, intends to infringe the B1 '899 patent as soon as such product is approved for marketing and sale by the FDA.

34. Defendant OHM's submission of the ANDA to the FDA, where the purpose of such submission is to obtain approval from the FDA to engage in the commercial manufacture, use and/or sale of an ibuprofen/pseudoephedrine product which is covered by the B1 '899 patent constitutes an act of infringement pursuant to 35 U.S.C. § 271 (e)(2)(A).

35. Defendant OHM's infringement of the B1 '899 patent has been and continues to be willful, wanton and deliberate, without license and with full knowledge and awareness of RVI's B1 '899 patent.

36. Unless restrained and enjoined by this Court, defendant OHM will continue its act of infringement. As a result, the damages to plaintiff RVI and its sole licensee AHP shall be substantial, continuing and irreparable.

37. Unless restrained and enjoined by this Court, defendant OHM's actions will encourage other pharmaceutical manufacturers to seek approval from the FDA to manufacture and sell a generic version of the ibuprofen/pseudoephedrine product covered by the B1 '899 patent resulting in further substantial and irreparable damage to plaintiff RVI and its sole licensee AHP.

38. A decision on whether the product for which defendant OHM seeks FDA approval infringes the B1 '899 patent will provide the parties with a determination of their respective rights and obligations upon which they can justifiably rely in assessing their future conduct.

39. In order to preserve the rights of RVI and AHP under the B1 '899 patent, and to minimize future damages to plaintiff RVI and its sole licensee AHP, the present action seeks a judgment declaring that defendant OHM's submission of the ANDA to the FDA infringes the B1 '899 patent and that the product for which defendant OHM is seeking FDA approval infringes the B1 '899 patent.

40. Plaintiff RVI has no adequate remedy at law.

RELIEF

WHEREFORE, Plaintiff RVI prays that:

- (a) This Court declare that defendant OHM's actions, if permitted to continue, constitute an infringement of the B1 '899 patent;

JAMES S. RUBIN
Attorney at Law
7004 Kennedy Blvd East-22D
West New York, N.J. 07093

Admitted in DC & NY
Not admitted in NJ

Phone 201.869.6151
Fax 201.869.1356

August 2, 1996

NAT
Return receipts providing
notification to Patent owner
3/12/96
NEW CORRESP
NC

Mr. Peter Rickman (via fax and US Mail)
FDA Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place--Room 150
Rockville, MD 20855

RE: ANDA 74-567
Patent Holder's Letter of July 31, 1996

Dear Mr. Rickman:

Ohm is in receipt of a courtesy copy of a letter dated July 31, 1996, from Mr. Mohl of Proctor and Gamble urging FDA to cease processing of Ohm's ANDA. (Letter enclosed.)

Certified copies of the statutory-required Notice letters were received by Richardson Vicks on July 1, 1996; and Whitehall Laboratories on July 11, 1996. (See enclosed copies of Return Receipts.)

Section 505(j)(4)(B)(iii) of the Act requires FDA to grant Ohm an immediate effective approval upon FDA's final review of our ANDA unless the Patent Holder institutes an infringement suit within the statutory 45-day period. [In addition, upon information and belief, Ohm is the first Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) applicant with a Paragraph IV Patent Challenge and we believe that we are entitled to all of the benefits of 505(j)(4)(B)(iv).]

This letter is to inform you that, as Ohm's counsel, I consider the Mohl letter to be baseless. Mohl's letter is rife with extraneous facts; but, is lacking in any legal application; and, in fact, is totally lacking in legal merit. The fact that the patent is being litigated elsewhere or by other parties is of no legal consequence under the Act.

[Furthermore, FDA's precedence is also illustrated by the Captopril situation wherein there were numerous ANDA's with Paragraph IV challenges, one of which received approval because of the patent holder's failure to sue within 45 days while a number of other ANDAs were litigating the same challenged patent.]

Ohm has met all of the requirements of the Act; and it would be both illegal and unconscionable for FDA, in any way whatsoever, to delay review of Ohm's application.

We request your immediate response so that we can consider any necessary further action if FDA decides to cease review and approval of Ohm's ANDA.

for OHM LABORATORIES, INC.
by its counsel



James S. Rubin

cc: Dr. Arun Heble, President
OHM Laboratories, Inc.
Attorney Charles Guttman, Patent
Counsel for Ohm
Douglas Mohl, Associate General Counsel
Proctor and Gamble

Procter & Gamble

Patent Division
The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road, Mason, Ohio 45040-9462

July 31, 1996

RECEIVED

Office of Generic Drugs (HFC-601)
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP

NC

AUG 6 1996

GENERIC DRUGS

Re: ANDA 74-567, Ohm Laboratories
NDA 19771, Ibuprofen/Pseudoephedrine Hydrochloride

PATENT OWNER'S OBJECTION TO ANDA APPLICANT CLAIMS OF PATENT
INVALIDITY, 21 CFR 314.94 AND REQUEST TO SUSPEND WORK ON ANDA 74,567

Dear Colleague:

This letter requests rejection by CDER of the filing in ANDA 74-567 of a statement of patent invalidity (505(j) (2) (A) (vii) (IV)) filed by Ohm Laboratories. The ANDA applicant has failed to satisfy 21 CFR §314.107(b) (3) because invalidity of the patent is still being contested. This letter by the patent owner seeks suspension of handling of the ANDA. No separate infringement suit is necessary at this point because the applicant is asserting that a ruling in pending litigation (to which the applicant was not a party) has authorized the applicant's ability to file the ANDA.

The ANDA applicant has the burden to show invalidity of the patent, and the matter of patent validity here is more convoluted than most such disagreements. The Court of Appeals for the Federal Circuit will have the dispute before it shortly and a decision is expected this winter. Pending the outcome of the Circuit Court's decision, no action should be taken on this ANDA because the legal issues of invalidity remain unresolved.

At issue is U.S. Patent 4,552,899 owned by a subsidiary of Procter & Gamble, expiring Nov. 12, 2002 (with the GATT extension 2004). This patent was successfully defended in a jury trial in 1995 (Civ. No. 93-556 SLR, D. Del., May 11, 1995) against parties other than Ohm Laboratories, and the trial judge later ruled contrary to the jury verdict. That ruling was appealed to the Court of Appeals for the Federal Circuit, where the oral arguments will be held soon. The issue on appeal is one of law rather than of fact, and Procter & Gamble expects that it will prevail on the controverted issues.

While the legal issues are still pending, the ANDA applicant has not satisfied its burden and the ANDA should not be processed. In light of the dependency of this applicant on the pending litigation, the proper remedy for OGD is to suspend review of the ANDA rather than await a further separate infringement suit. Please contact the undersigned at (513)622-3991 with any questions.

Very truly yours,

THE PROCTER & GAMBLE COMPANY



Douglas C. Mohl
Associate General Counsel - Patents
Health Care Division

CC: DLS
Rickman
Here

MORGAN & FINNEGAN, L.L.P.

A Registered Limited Liability Partnership

345 PARK AVENUE
NEW YORK, NEW YORK 10154-0053

TEL: (212) 758-4800

TELEX 421792

FACSIMILE: (212) 751-6849

WASHINGTON OFFICE

1289 PENNSYLVANIA AVENUE, N.W.
SUITE 960

WASHINGTON, D.C. 20004

TEL: (202) 857-7887

FACSIMILE: (202) 657-7929

WRITER'S DIRECT DIAL NUMBER:

JOHN D. FOLEY
JOHN A. DIAZ
THOMAS P. DOWLING
JOHN C. VASSIL
HEN H. ROTERT
Y A. EWERT†
I. PFEFFER
C. MARCUS
L. E. PAULSON
STEPHEN R. SMITH
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J. ROBERT DAILEY
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JOHN P. SINNOTT
NED W. BRANTHOVER
EUGENE C. RZUCIDLO*†
COUNSEL

RESIDENT PARTNERS IN WASHINGTON
HARRY F. MANBECK, JR.*†
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CHRISTOPHER J. HAMATY*
KATHRYN E. DIAZ*
ALANA G. FIRESTER

SCIENTIFIC ADVISORS
KATHRYN M. BROWN, Ph.D.
LESLIE A. SERUNIAN, Ph.D.
DOROTHY R. ALUTH, Ph.D.
DAVID V. ROSSI, Ph.D.
CAROL GRUPPI, Ph.D.
RICHARD W. BORK, Ph.D.

*NOT ADMITTED IN NEW YORK FOREIGN LAW ADVISOR
†ADMITTED IN WASHINGTON, D.C. RYOSUKE FUJIMOTO

FAX

TO: United States Food And Drug Administration
Company Name

Office of Generic Drugs (HFD-6000)
Attention

(301) 594-0183

Telephone Phone Number
(301) 594-0340

Office Phone Number

FROM: NEW YORK OFFICE

John F. Sweeney, Esq.

Sender

Number of Pages: 12 (& Cover)

Client/Matter No.: 0616-4090

Please confirm receipt: Yes No

COMMENTS:

THE DOCUMENT(S) ACCOMPANYING THIS FACSIMILE TRANSMISSION CONTAINS INFORMATION FROM THE LAW FIRM OF MORGAN & FINNEGAN WHICH IS CONFIDENTIAL AND/OR LEGALLY PRIVILEGED. THE INFORMATION IS INTENDED ONLY FOR THE USE OF THE INDIVIDUAL OR ENTITY NAMED ON THIS TRANSMISSION SHEET. IF YOU ARE NOT THE INTENDED RECIPIENT, YOU ARE HEREBY NOTIFIED THAT ANY DISCLOSURE, COPYING, DISTRIBUTION OR THE TAKING OF ANY ACTION IN RELIANCE ON THE CONTENTS OF THIS FAXED INFORMATION IS STRICTLY PROHIBITED, AND THE DOCUMENT(S) SHOULD BE RETURNED TO THIS FIRM IMMEDIATELY. IF YOU HAVE RECEIVED THIS FACSIMILE IN ERROR, PLEASE NOTIFY US BY TELEPHONE IMMEDIATELY SO THAT WE CAN ARRANGE FOR THE RETURN OF THE ORIGINAL DOCUMENTS AT NO COST TO YOU.

28 U.S.C. §§ 1331 and 1338. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(c) and 1400(b).

PARTIES

2. Plaintiff RVI is a corporation organized under the laws of the State of Delaware and conducts business within this judicial district.

3. Upon information and belief, defendant OHM is a corporation organized under the laws of the State of New Jersey and has an office and principal place of business at 1385 Livingston Avenue, North Brunswick, New Jersey.

BACKGROUND

4. Plaintiff RVI is the owner by assignment of original United States Patent No. 4,552,899 (the "'899 patent") and Re-examination Certificate No. B1 4,552,899 (the B1 "'899 patent") for an invention entitled "Cough-Cold Mixtures Comprising Nonsteroidal Anti-Inflammatory Drugs". The '899 patent, which issued on November 12, 1985, was subjected to two re-examination proceedings in the United States Patent and Trademark Office. The re-examinations were consolidated and resulted in the issuance of the B1 '899 patent on October 20, 1992. A copy of the reexamined B1 '899 patent and original '899 patent is attached as Exhibit A.

5. The B1 '899 patent has thirty (30) claims, Claims 21-50. Claims 21-23, 25-26, 28, 31-37, 40-42 and 44-48 are directed to pharmaceutical compositions and methods of treatment with ibuprofen and pseudoephedrine as active ingredients and specifically to a composition containing 200 mg ibuprofen and 30 mg pseudoephedrine.

6. In September 1989, American Home Products Corp. ("AHP") received approval of its New Drug Application ("NDA") from the United States Food and Drug Administration ("FDA") to market a product containing 200 mg ibuprofen and 30 mg pseudoephedrine. AHP's product was initially marketed under the tradename Co-Advil. The name of the product was subsequently changed to Advil® Cold & Sinus.

7. In October 1992, in the United States District Court for the District of Delaware (Civil Action No. 92-634), RVI commenced a patent infringement action against AHP alleging that AHP's manufacture and sale of the Advil® Cold & Sinus ibuprofen/pseudoephedrine product infringed the B1 '899 patent.

8. The action was settled by the parties prior to trial. In the settlement, RVI granted AHP a sole license under the B1 '899 patent, and AHP granted RVI rights under its NDA.

9. On or about September 1993, The Upjohn Company ("Upjohn") commercially introduced a product having 200 mg ibuprofen and 30 mg pseudoephedrine under the tradename Motrin® IB Sinus.

10. On or about September 1993, McNeil-PPC and Johnson & Johnson (collectively "McNeil") commercially introduced a product having 200 mg ibuprofen and 30 mg pseudoephedrine under the tradename Sine-Aid® IB.

11. In July 1994 RVI began selling a product having 200 mg ibuprofen and 30 mg pseudoephedrine. That product is marketed under the tradename DayQuil® Sinus Pressure and Pain with Ibuprofen .

12. As of 1993, the ibuprofen/pseudoephedrine product covered by the B1 '899 patent had gained a strong market position and had established annual sales of approximately \$50 million.

13. In December 1993, in the United States District Court for the District of Delaware (Civil Action No. 93-556), RVI commenced a patent infringement action against Upjohn and McNeil alleging that the manufacture and sale of Upjohn's Motrin® IB Sinus ibuprofen/pseudoephedrine product and Upjohn's Sine-Aid® IB ibuprofen/pseudoephedrine product infringed Claims 36, 37, 47 and 48 of the B1 '899 patent.

14. The District Court ruled as a matter of law that Upjohn's Motrin® IB Sinus product and McNeil's Sine-Aid® IB product infringed Claims 36, 37, 47 and 48 of the B1 '899 patent.

15. Upjohn and McNeil contended that Claims 36, 37, 47 and 48 of the B1 '899 patent were not valid under 35 U.S.C. § 103 for obviousness and/or not valid under 35 U.S.C. § 102(g) because of an alleged prior invention by AHP.

16. After a twelve (12) day trial, the jury returned verdicts in favor of RVI that Upjohn and McNeil had failed to prove by clear and convincing evidence that Claims 36, 37, 47 and 48 of the B1 '899 patent were not valid under 35 U.S.C. § 103 and/or 35 U.S.C. § 102(g) and awarded RVI damages based on a reasonable royalty of 7% for Upjohn's and McNeil's infringing sales.

17. On May 10, 1995, the District Court entered judgment in favor of RVI based on the jury verdicts.

18. Subsequently, Upjohn and McNeil filed motions for judgment as a matter of law pursuant to Rule 50(b), Fed. R. Civ. P., requesting that the District Court, *inter alia*, enter a judgment that Claims 36, 37, 47 and 48 of the B1 '899 patent are not valid.

19. On January 17, 1996, eight months after the jury verdict and the original judgment, the District Court, without entertaining oral argument, granted judgment as a matter of law that Claims 36, 37, 47 and 48 of the B1 '899 patent are not valid for obviousness and for prior invention.

20. On February 6, 1996, RVI timely filed a Notice of Appeal to the United States Court of Appeals for the Federal Circuit. Upjohn and McNeil did not cross-appeal the District Court's judgment that their respective products infringe the B1 '899 patent.

21. On appeal, RVI demonstrated that in entering judgment as a matter of law that the B1 '899 is not valid, the District Court, *inter alia*, improperly substituted its own views for those of the jury, used the wrong legal standard in analyzing the alleged prior invention of AIMP, and impermissibly selected evidence to buttress its own opinion while ignoring the substantial evidence which supports the jury verdicts. RVI's arguments to the Court of Appeals for the Federal Circuit demonstrate RVI's good faith belief that Claims 36, 37, 47 and 48 of the B1 '899 patent are valid and that the Court of Appeals will ultimately vacate the District Court's judgment of invalidity and reinstate the jury verdicts.

22. Briefing by the parties was completed in July 1996. The Joint Appendix was filed on August 1, 1996. The Court of Appeals should schedule oral

argument shortly and a decision could be expected within the next six months. In view of the appeal addressing the validity of certain claims of the B1 '899 patent, RVI is agreeable to staying this action pending the decision by the Court of Appeals for the Federal Circuit. Thus, RVI will file a motion to stay this action in the near future.

PROCEEDINGS BEFORE THE FDA

23. Pursuant to the Food, Drug and Cosmetic Act ("FDCA") [*i.e.*, 21 U.S.C. § 321 *et seq.*], the FDA is responsible for determining whether a generic drug product should be approved for sale.

24. Pursuant to Section 505(j) of the FDCA [*i.e.*, 21 U.S.C. § 355(j)], a pharmaceutical manufacturer seeking approval to market a generic version of a patented drug may submit an Abbreviated New Drug Application ("ANDA") to the FDA.

25. Section 505 (j)(2)(A)(vii)(I)-(IV) of the FDCA [*i.e.*, 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV)] requires that an applicant submitting an ANDA must certify one of four things: (1) that the drug for which the ANDA is submitted has not been patented ("paragraph I certification"); (2) that the patent on such drug has expired ("paragraph II certification"); (3) the date on which the patent on such drug will expire if it has not yet expired ("paragraph III certification"); or (4) that the patent on such drug is not valid or will not be infringed by the manufacture, use and/or sale of the drug for which the ANDA has been submitted ("paragraph IV certification"). The certification requirements of Section 505(j) of the FDCA are also set forth in 21 C.F.R. § 314.107(b)(1)(i)-(iv).

26. Section 505(j)(2)(B) of the FDCA [*i.e.*, 21 U.S.C. § 355(j)(2)(B)] requires that when an applicant submits an ANDA containing a paragraph IV certification,

the ANDA applicant must provide the owner of the relevant patent notice of the applicant's submission of the certification to the FDA.

27. Section 505(j)(4)(B)(iii) of the FDCA [*i.e.*, 21 U.S.C. § 355(j)(4)(D)(iii)] requires that if the ANDA contains a paragraph IV certification, and all applicable scientific and regulatory requirements have been met, the FDA's approval of the ANDA "shall be made effective immediately" unless the patent owner brings an action for infringement pursuant 35 U.S.C. § 271(e)(2)(A) within forty-five (45) days of receiving notice from the ANDA applicant that an ANDA has been submitted to the FDA. This provision of the FDCA is also set forth in 21 C.F.R. § 314.107(b)(3).

28. Pursuant to 35 U.S.C. § 271(e)(2)(A), "[i]t shall be an act of infringement to submit . . . an application under Section 505(j) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. § 355(j)] . . . for a drug claimed in a patent or the use of which is claimed in a patent . . . if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent."

29. Section 505(j)(4)(B)(iii)(I)-(III) [*i.e.*, 21 U.S.C. § 355(j)(4)(B)(iii)(I)-(III)] requires that once the patent owner commences an infringement action pursuant to 35 U.S.C. § 271(e)(2)(A), the FDA shall suspend approval of the ANDA until the earliest of three dates: (i) the date of the court's decision holding that the patent is not valid or not infringed; (ii) the date the patent expires if the court determines that the patent is infringed; or (iii) subject to modification by the court, thirty months from the patent owner's receipt of notice of the ANDA applicant's filing of a paragraph IV certification with the FDA.

30. Under 21 C.F.R. § 314.107(e), the court decision is one from which no appeal can be or has been taken.

COUNT FOR PATENT INFRINGEMENT

31. In a letter dated on June 28, 1996, defendant OHM notified plaintiff RVI of its submission of its paragraph IV certification to the FDA. RVI received OHM's letter on July 1, 1996.

32. Defendant OHM's letter dated June 28, 1996 states that OHM has submitted an ANDA to the FDA "in order to obtain approval to engage in the commercial manufacture, use or sale" of a product containing 200 mg ibuprofen and 30 mg pseudoephedrine prior to the expiration of the B1 '899 patent.

33. Based on its June 28, 1996 letter, Defendant OHM is prepared to manufacture and sell a product containing 200 mg ibuprofen and 30 mg pseudoephedrine and, intends to infringe the B1 '899 patent as soon as such product is approved for marketing and sale by the FDA.

34. Defendant OHM's submission of the ANDA to the FDA, where the purpose of such submission is to obtain approval from the FDA to engage in the commercial manufacture, use and/or sale of an ibuprofen/pseudoephedrine product which is covered by the B1 '899 patent constitutes an act of infringement pursuant to 35 U.S.C. § 271 (e)(2)(A).

35. Defendant OHM's infringement of the B1 '899 patent has been and continues to be willful, wanton and deliberate, without license and with full knowledge and awareness of RVI's B1 '899 patent.

36. Unless restrained and enjoined by this Court, defendant OHM will continue its act of infringement. As a result, the damages to plaintiff RVI and its sole licensee AHP shall be substantial, continuing and irreparable.

37. Unless restrained and enjoined by this Court, defendant OHM's actions will encourage other pharmaceutical manufacturers to seek approval from the FDA to manufacture and sell a generic version of the ibuprofen/pseudoephedrine product covered by the B1 '899 patent resulting in further substantial and irreparable damage to plaintiff RVI and its sole licensee AHP.

38. A decision on whether the product for which defendant OHM seeks FDA approval infringes the B1 '899 patent will provide the parties with a determination of their respective rights and obligations upon which they can justifiably rely in assessing their future conduct.

39. In order to preserve the rights of RVI and AHP under the B1 '899 patent, and to minimize future damages to plaintiff RVI and its sole licensee AHP, the present action seeks a judgment declaring that defendant OHM's submission of the ANDA to the FDA infringes the B1 '899 patent and that the product for which defendant OHM is seeking FDA approval infringes the B1 '899 patent.

40. Plaintiff RVI has no adequate remedy at law.

RELIEF

WHEREFORE, Plaintiff RVI prays that:

- (a) This Court declare that defendant OHM's actions if permitted to continue, constitute an infringement of the B1 '899 patent;

JAMES S. RUBIN
Attorney at Law
7004 Kennedy Blvd East-22D
West New York, N.J. 07093

Admitted in DC & NY
Not admitted in NJ

Phone 201.869.6151
Fax 201.869.1356

NAI
Patent cert III to
Patent cert. IV challenger
patent. IS/

NEW CORRESP

May 29, 1996

Rubin will provide
notification to Patent
holder. IS/
5/29/96

Mr. Peter Rickman (via fax and US Mail)
FDA Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place--Room 150
Rockville, MD 20855

RE: Ibuprohm Cold & Sinus Caplets & Tablets
Ibuprofen 200mg; Psuedoephedrine HCl 30mg
ANDA 74-567
SECTION III

RECEIVED

MAY 29 1996

AMENDED PATENT CERTIFICATION

PARAGRAPH IV CERTIFICATION

GENERIC DRUGS

III. a. Paragraph IV Patent Certification

Pursuant to section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, as amended (the Act), Ohm Laboratories, Inc. (OHM), by and through its counsel, James S. Rubin, herein makes the following Amended Patent Certification:

1. The listed drug product, as it appears at page 3-313 of the 16th Edition of Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), is ADVIL COLD AND SINUS, N19771. According to page AD 28 of the 16th Edition of the Orange Book, there is one (1) listed patent: 4,552,899.

2. OHM previously filed a Paragraph III certification as to that patent by indicating that they will market their product only after expiration of the listed patent. OHM now amends its Patent Certification as follows:

ANDA 74-567
Paragraph IV Patent Certification

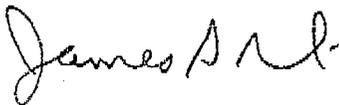
Paragraph IV Patent Certification

We herein certify pursuant to section 505(j)(2)(A)(vii)(IV) of the Act and 21 CFR 314.94(a)(12) that patent number 4,552,899 is invalid, unenforceable, or will not be infringed by OHM's manufacture, use, or sale of the new drug (Ibuprofen 200mgs; Pseudoephedrine HCl 30mgs; Oral Tablet) for which this application is submitted. [That patent has a listed expiration date of November 12, 2002, as indicated at page AD28 of the 16th Edition of the Orange Book.]

Pursuant to section 505(j)(2)(B) of the Act and 21 CFR 314.94 and 314.95, this is to certify that OHM will give the notice required by section 505(j)(2)(B)(ii) of the Act and comply with 21 CFR 314.95(a) with respect to providing to each owner of the patent which is the subject of the 505(j)(2)(A)(vii)(IV) patent certification above or to the designated representative(s) and to the holder of the approved application under section 505(b) of the Act for the listed drug that is claimed by the patent and for which the applicant is seeking approval; and will comply with the requirements under 21 CFR 314.95(c) with respect to the content of the notice.

A copy of the applicable pages from the 16th Edition of Approved Drug Products with Therapeutic Equivalence Evaluations (pages AD28 and 3-313) where the patent and exclusivity information appear, are attached.

for OHM LABORATORIES, INC.
by its counsel



James S. Rubin

cc: Dr. Arun Heble, President
OHM Laboratories, Inc.



NAI.
W. Rickman
7/25/96

July 18, 1996

NEW CORRESP
NC

RECEIVED

JUL 25 1996

GENERIC DRUGS

Mr. Peter Rickman
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place - Room 150
Rockville, MD 20855

RE: IBUPROHM Cold & Sinus Caplets & Tablets
(Ibuprofen 200 mg/Pseudoephedrine HCl 30 mg)
ANDA 74-567
PARAGRAPH IV PATENT CERTIFICATION

Dear Mr. Rickman:

Enclosed please find two (2) copies of the return receipts from Richardson-Vicks, Inc. and Whitehall Laboratories, Inc. regarding the Notification Letter on the above captioned ANDA.

Best Regards,

Arun R. Heble
President & COO

ARH/amb

ENCLOSURE

pharmaceutical quality you can depend on...

5/29/26
fax

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pages of trade

secret and/or

confidential

commercial

information



May 29, 1996

Peter Rickman
CSO
Office of Generic Drugs
Food & Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: IBUPROHM COLD & SINUS CAPLETS AND TABLETS
(IBUPROFEN 200 mg/PSEUDOEPHEDRINE HCl 30 mg)
ANDA 74-567

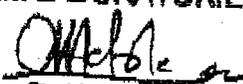
Dear Mr. Rickman:

This is to authorize Mr. James S. Rubin to represent us in all matters on the above captioned ANDA.

Best Regards,

Sincerely,

OHM LABORATORIES, INC.


Arun R. Heble
President & C.O.O.

ARH/amb

pharmaceutical quality you can depend on.



ohm laboratories, inc.

April 30, 1996

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/A/C

RECEIVED

MAY 06 1996

GENERIC DRUGS

RE: IBUPROHM COLD AND SINUS CAPLETS AND TABLETS
(IBUPROFEN 200 mg/PSEUDOEPHEDRINE HCl 30 mg)
ANDA 74-567

Gentlemen:

Reference is made to our abbreviated new drug application submitted on October 31, 1994 pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act, for Ibuprofen and Pseudoephedrine Hydrochloride Tablets, 200 mg/30 mg.

Reference is also made to your December 21, 1994 letter refusing to file our application, our subsequent amendment dated January 24, 1995, and your most recent letter dated July 25, 1995 including chemistry and labeling deficiencies.

Our response to your July 25, 1995 letter is as follows:

SECTION A (CHEMISTRY DEFICIENCIES)

1. A revised Patent Certification and Exclusivity Statement is attached for inclusion under SECTION III.

2(a).

[]

this section. All ingredients have remained identical to those submitted with our original application.

MAILING:
P.O. Box 7397
North Brunswick, NJ 08902

OFFICE:
1385 Livingston Avenue
North Brunswick, NJ 08902

Tel: 908-247-6832
Tel: 800-527-6481
Fax: 908-247-0268

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secret and/or

confidential

commercial

information

ANDA 74-567

Ohm Laboratories Inc.
Attention: Arun R. Heble
P.O. Box 279
Franklin Park, NJ 08823

JUL 25 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated October 31, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ibuprofen and Psuedoephedrine Hydrochloride Tablets, 200 mg/30 mg.

Reference is also made to your amendment dated January 24, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. The information provided in your Patent Certification and Exclusivity Statement is incorrect. N19771 001 is not a patent number but an NDA number. Please revise your Patent Certification and Exclusivity Statement to provide correct information.
2. The following comments pertain to your components and composition:
 - a. The following ingredients were identified in the labeling section of the application but did not appear in the components and composition section: FD&C Blue #2 _____, FD&C Red #40 _____, FD&C Yellow #6 _____, Iron Oxides, Lecithin, Pharmaceutical Glaze, Povidone, Sodium Benzoate, and Titanium Dioxide. Please comment.
 - b. Please provide the components in and the quantitative composition of all _____ materials.
 - c. The components and composition section indicated that _____ and _____, would be used to _____ these drug products. However, the batch records indicate the use of _____
_____ Please comment.

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13. []

14. The following comments pertain to the stability section of your application:

- a. Please add a test method and limit for impurities to your stability protocol.
- b. Please revise your stability data report forms so that the source of packaging materials is identified, especially for the case of unit dose packaging materials.
- c. Please identify the source of the unit dose blister packaging materials for which stability data was provided in your application.

d. []

15. The Environmental Assessment statement lacks quantitative data as required by 21 CFR 25.31. Please provide an appropriate Environmental Assessment statement. You may wish to evaluate your eligibility under 21 CFR 25.24(c)(1).

16. Please confirm that both of these products will be imprinted.

17. Please provide an updated 356h form listing all of the DMFs referenced in your application.

B. Labeling Deficiencies (DRAFT LABELING)

General Comments:

1. The Agency recently published the final monograph for OTC nasal decongestant products. The monograph applies to combination products as well as single ingredient products. In it, the Agency modified labeling language in INDICATIONS and WARNINGS in §341.80. The final rule was published in the FEDERAL REGISTER on August 23, 1994. The effective date for the changes described in this final rule is August 23, 1995. Please make appropriate changes in your labeling.

2. Throughout your labeling for this product, define "caplet", as "capsule-shaped tablet", rather than

At the bottom of your insert, include the name and place of business as described in 21 CFR 201.1. Also, include a revision date.

Please revise your labels and labeling, then prepare and submit draft labels and labeling.

C. In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. ~~_____~~

2. Concerning your request for a 2-year expiration period for product packaged in bottles to start at the day of release testing (NMT 30 days since the date of manufacture) and for a 2-year expiration period for product packaged in blisters to start from the date of packaging (provided it is NMT 60 days since the day of release testing, or in other words NMT 90 days since the date of manufacture), we have the following comments:

a. ANDAs are generally approved with a tentative expiration period of 24 months on the basis of accelerated stability data. If long term room temperature stability data from the first three production batches do not support a 24-month expiration period, a shorter expiration period should be substituted.

b. It is up to the local FDA field office to determine if your method for calculating expiration dates is consistent with cGMPs.

3. 21 CFR 314.50(g)(1) states that " a reference to information submitted previously is required to identify the file name, reference number, volume and page number in the Agency's records where the information can be found." Reference is also made to 21 CFR 314.420(d).

Please ensure that all letters of authorization provided to you by the DMF holders for inclusion in the ANDA are complete in this regard.

4. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with cGMPs at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours */S/* 7/28/95
R. ... Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: 74-567
DUP Jacket
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-623/JSmith/7/5/95
HFD-623/JClark for RKishore */S/* 7/11/95
HFD-613/CZimmerman for CH */S/* 7/12/95
HFD-617/JWilson/7/12/95
x:\WPFILE\BRANCH1\SMITH\N74567L1 */S/* 7/17/95
F/T by: gp/7/17/95
C:\WPFILES_ANDAS\N74567L1 */S/* 7-18-95

NOT APPROVABLE: MAJOR AMENDMENT

ANDA 74-567

Ohm Laboratories, Inc.
Attention: Arun R. Heble
P.O. Box 279
Franklin Park, NJ 08823

MAR 10 1995

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated December 21, 1994, and your amendment dated January 24, 1995.

NAME OF DRUG: Ibuprofen and Pseudoephedrine Hydrochloride Tablets
USP, 200 mg/30 mg

DATE OF APPLICATION: October 31, 1994

DATE OF RECEIPT: November 10, 1994

DATE ACCEPTABLE FOR FILING: January 27, 1995

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

James Wilson
Consumer Safety Officer
(301) 594-0310

Sincerely yours,

JS

3/10/95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

ANDA 74-567

Food and Drug Administration
Rockville MD 20857

Ohm Laboratories, Inc.
Attention: Arun R. Heble
P.O. Box 279
Franklin Park, NJ 08823

DEC 21 1994

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated October 31, 1994, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Ibuprofen and Pseudoephedrine Hydrochloride Tablets, 200 mg/30 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

[REDACTED]

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

[REDACTED]

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours

12/20/94
15/
Gordon R Johnston
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Whitehall Laboratories
885 Third Avenue
New York, New York 10017-4078
Telephone (212) 878-5500

APPEARS THIS WAY
ON ORIGINAL



October 8, 1993

NDA 19-771
Advil® Cold & Sinus, Dristan Sinus and Dimetapp Sinus
Supplemental Application: TIME SENSITIVE PATENT
INFORMATION

Food & Drug Administration
Center for Drug Evaluation and Research
Document Control Room 98-23
5600 Fishers Lane
Rockville, MD 20857-1706

Dear Sir/Madam

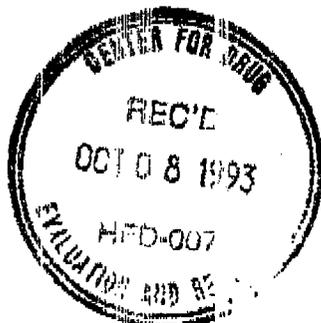
Please refer to Whitehall Laboratories ("whitehall") NDA 19-771 for Advil Cold & Sinus, Dristan Sinus and Dimetapp Sinus (ibuprofen and pseudoephedrine) caplets. Whitehall herewith submits time sensitive patent information concerning patent number B1 4,552,899 which claims the composition or use of the drug products subject to NDA 19-771.

This information is being submitted herewith in light of the dismissal on September 8, 1993 by the United States District Court for the District of Delaware of certain litigation relating to claims of infringement of this patent by these products, Richardson-Vicks, Inc. v. American Home Products Corporation and Whitehall Laboratories, Inc., C.A. No. 92-634 (SLR).

If you have any questions regarding this submission, please contact the undersigned at (212) 878-5493.

Sincerely yours,
WHITEHALL LABORATORIES

John R. Jacobs
Vice President, Regulatory
Affairs



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ADDITIONAL PATENT INFORMATION

1. Patent number 4,552,899 was issued by the Patent Office on November 12, 1985.

2. On August 24, 1990 and January 2, 1991, requests for reexamination of the patent were filed in the United States Patent and Trademark Office which led to the initiation thereafter of reexamination proceedings by that office.

3. On October 20, 1992, the Reexamination Certificate for United States Patent No. 4,552,899 was issued with modified claims.

4. On October 30, 1992, Richardson-Vicks, Inc. filed a complaint against American Home Products Corporation in the United States District Court for the District of Delaware for infringement of the B1 4,552,899 patent by products subject to NDA 19-771 [Civil Action No. 92-634 (SLR)].

5. On August 23, 1993, as a result of settlement negotiations, American Home Products Corporation and Whitehall Laboratories, Inc. were licensed under patent B1 4,552,899.

6. On September 8, 1993, Civil Action No. 92-634 (SLR) was dismissed by the United States District Court for the District of Delaware.

SUPPLEMENT

TIME SENSITIVE PATENT INFORMATION

The following is new information regarding a patent which claims composition and use of drug products covered by this New Drug Application.

The patent covering the drug is Patent No. B1 4,552,899.

Date of expiration: November 12, 2002

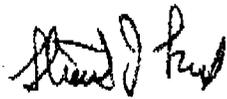
Type of patent: drug product and method of use

Name of patent holder: Richardson-Vicks, Inc.

CERTIFICATION

The undersigned certifies that the drug and the formulation or composition of ibuprofen/pseudoephedrine HCl tablets/caplets subject to NDA 19-771 and their use is claimed by patent number B1 4,552,899. These products are currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

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Stuart J. Land
Attorney for Whitehall
Laboratories

10-24-94 04:05 PM

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Whitehall Laboratories
685 Third Avenue
New York, New York 10017-4076
Telephone (212) 979-6600



October 8, 1993

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 214
5600 Fishers Lane
Rockville, MD 20857-1706

Re: TIME SENSITIVE PATENT INFORMATION
Ibuprofen/Pseudoephedrine HCl
Advil® Cold and Sinus/Dristan Sinus/
Dimeapp Sinus

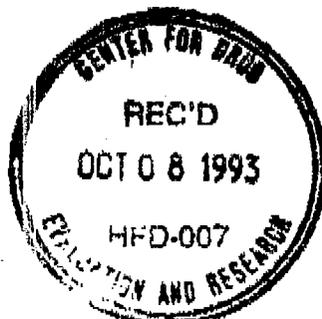
Dear Sir/Madam:

I am enclosing the following time sensitive patent information which has also been filed as a supplemental application to NDA 19-771. This filing is being made in light of the dismissal on September 8, 1993 by the United States District Court for the District of Delaware of certain litigation relating to claims of infringement of this patent by these products, Richardson-Vicks, Inc. v. American Home Products Corporation and Whitehall Laboratories, C.A. No. 92-634 (SLR).

Sincerely,

John R. Jacobs HBY

John R. Jacobs



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