CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

CORRESPONDENCE

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

WHITEHALL ROBINS

January 24, 2000

SUPPL NEW CORRESP
SE1-005 - NC

NDA 20-402/S-005
Advil® Migraine Liqui-Gels
(Solubilized ibuprofen, 200 mg)

General Correspondence: Labeling Amendment - Clarification of Labeling submitted 1/21/00

Charles J. Ganley, MD. Director
Division of OTC Drug Products (HFD 560)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Ganley:

Reference is made to Whitehall-Robins Healthcare ("Whitehall-Robins") NDA 20-402/S-005, which provides for the OTC use of Advil® Migraine Liqui-Gels (200 mg solubilized ibuprofen capsules) to treat migraine. In particular, reference is made to the Amendment to Labeling submitted on 1/21/00.

In this amendment, we proposed the following directions:

- do not take more than directed
- adults: take 1 capsule
- if migraine does not respond to 1 capsule within 1 hour, you may take one more capsule
- with experience, you may find you need 2 capsules to treat your migraine
- the smallest effective dose should be used
- if symptoms persist or get worse, call a doctor
- under 18 years of age: call a doctor before use

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However, we have recently noticed that these Directions are not stated as such on some of the labeling components that were submitted (in particular, the 20s, 40s,

80, 135s, and 200s size cartons in the non-column format). Please note that this was not our intention and that the Directions as written above should be incorporated on all of the labels that require the Directions to be stated. We apologize for this oversight and for any confusion or problems this may have caused.

If you have any comments or questions regarding this amendment, please contact the undersigned at (973) 660-5753 or Ms. Mary Davis at (973) 660-5825 [Fax: (973) 660-7187].

Sincerely,
WHITEHALL-ROBINS HEALTHCARE

Mary A Davis

for Sharon C. Heddish
Vice President,
Regulatory Affairs Worldwide

cc: K. Rothschild

DUPLICATE

SE1-005/BZ

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

12/7/99 noted

WHITEHALL ROBINS

November 19, 1999

NDA 20-402/S-005
Advil® Liqui-Gels®
(Ibuprofen 200 mg)

NDA SUPPL AMENDMENT

Amendment to Supplement 005 (Migraine Headache Indication): Clinical and Labeling

Charles J. Ganley, MD, Director
Division of OTC Drug Products (HFD 560)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Ganley:

Please refer to Whitehall-Robins' NDA 20-402/S-005 which provides for the OTC use of Advil® Migraine (200 mg solubilized ibuprofen capsules) for the treatment of mild to moderate migraine headache. Reference is also made to a conversation between Ms. Mary Davis of Whitehall-Robins and Mr. Kerry Rothschild of the Division regarding the Agency's agreement to Whitehall-Robins submitting data to support an expanded claim "treats migraine" for Advil® Migraine. Based on that discussion, it is our understanding that submitting these data will not affect the review clock.

This submission presents efficacy and safety data from a subgroup of subjects enrolled in the two migraine studies AM-98-01 and AM-98-02. This subgroup consists of subjects who reported severe migraine pain and severe limitation of activity at baseline. The data demonstrate that ibuprofen 200 mg and 400 mg administered as liquigels to subjects with severe migraine are effective in relieving migraine headache compared to placebo. In addition, both dosages improved the quality of life by significantly reducing activity limitation and significantly reducing multiple ancillary symptoms during a severe migraine episode as compared to placebo. The results in the severe subgroup were consistent with those obtained in the overall study population and indicate that ibuprofen liquigels 200 - 400 mg provide effective relief of migraine pain and associated symptoms. A summary of the severe subgroup analysis is submitted herewith as an amendment to Supplement 005 (See Attachment 1). To facilitate review of these data, the document follows the format of the Integrated Summary of Effectiveness. Based on these data, Whitehall-Robins request approval of the indication "treats migraine" for Advil Migraine at doses of 200–400 mg.

Whitehall-Robins
Five Giralda Farms
Madison, NJ 07940-087[illegible]
Telephone (973) 660-5[illegible]0
Website address: http[illegible]ealthfront.com

WHITEHALL ROBINS

September 30, 1999

NDA NO. 20402 REF. NO. 006
NDA SUPPL FOR SCS

NDA 20-402
Advil® Liqui-Gels®
(Ibuprofen 200mg)

Supplemental Application:
Chemistry, Manufacturing and Controls

Charles Ganley, M.D., Director
Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Ganley:

Reference is made to new drug application (NDA) 20-402 sponsored by Whitehall-Robins Healthcare for Advil® Liqui-Gels® (Ibuprofen 200 mg). Reference is also made to our telefaxes dated January 28, 1999 and March 11, 1999 requesting FDA feedback on proposed improvements to the liquigel manufacturing process (i.e. use of "in-line" ribbon printing, use of an alternate ink, and elimination of a naphtha wash). The Division's opinion (as noted in a March 1, 1999 memorandum from Dr. Charlotte Yaciw to Dr. Hasmukh Patel) was that a prior approval supplement would be necessary to provide for the proposed modifications to the manufacturing process. Please note that the requirements for this submission were discussed with the Division during a teleconference held April 15, 1999. The enclosed supplement is submitted in accordance with the FDA guidance provided March 1, 1999 and April 15, 1999.

Whitehall-Robins hereby certifies that a copy of this submission has been forwarded to the FDA District Offices in North Brunswick, NJ and Buffalo, NY. If you have any questions or comments, please contact the undersigned at (973) 660-6896 [fax (973) 660-7162] or Susan Beavis at (973) 660-5068 [fax (973) 660-7187)].

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Susan Beavis
for Ken Warner
Director, Regulatory Affairs CMC

ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-402/S-006

OCT 7 1999

Whitehall-Robins Healthcare
5 Giralda Farms
Madison, NJ 07940

Attention: Ken Warner
Director, Regulatory Affairs CMC

Dear Mr. Warner:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Advil® Liqui-Gels® (ibuprofen 200mg)

NDA Number: 20-402

Supplement Number: S-006

Date of Supplement: September 30, 1999

Date of Receipt: October 1, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on November 30, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Over-the-Counter Drug Products, HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Maria Rossana R. Cook, M.B.A.
Chief, Project Management Staff
Division of Over-the-Counter Drug Products, HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-402/S-005

AUG 6 1999

Whitehall-Robins
Attention: Sharon Heddish
Director, Regulatory Affairs
Five Giralda Farms
Madison, NJ 07940-0871

Dear Ms. Heddish:

Please refer to your supplemental new drug application (supplemental NDA) dated May 14, 1999, received May 17, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil Liqui-Gels® (solubilized ibuprofen) capsules, 200mg. This supplemental NDA proposes a new indication for the treatment of mild to moderate migraine headache. The supplemental NDA further proposed that the product be a brown oval liquid filled gel, rather than the green oblong oval liquid filled gel currently marketed.

Please also refer to your additional communication dated June 16, 1999, addressing issues discussed in our June 15, 1999 teleconference.

In your letter of June 16, 1999, you note that Whitehall proposed a bioequivalence study (protocol PV 96-08) several years ago which would compare the green oblong Liqui-Gels® with the brown oval Liqui-Gels®. You also note that the FDA pharmacokinetics reviewer, Dr. Bashaw, suggested that the ibuprofen suspension should be the reference standard rather than the green oblong Liqui-Gels®. In providing this information, you failed to note the context in which this study was conducted. At the time, you were attempting to gain approval of the brown oval Liqui-Gels®. In order to do this, you needed to provide a bioequivalence study that compared the brown oval Liqui-Gels® to the reference listed drug. The reference listed drug at that time was the ibuprofen suspension. A bioequivalence study comparing the brown oval Liqui-Gels® to the green oblong Liqui-Gels® without including the reference listed drug (ibuprofen suspension) would not have led to an approval of the brown oval Liqui-Gels®. Had you also wanted to show that the brown oval Liqui-Gels® were bioequivalent to the green oblong Liqui-Gels®, you would have had to include the green oblong Liqui-Gels® in the study. Because this was not your intent at the time, you apparently chose not to include the green oblong Liqui-Gels® in study PV 96-08. Based on your intent at the time, study PV 96-08 compared the brown oval Liqui-Gels® with the reference listed drug, ibuprofen suspension. For the record,

you reached an agreement with the FDA on a bioequivalence program that would lead to the approval of the brown oval Liqui-Gels® . You did not reach an agreement with the FDA on a program that would show bioequivalence of the green oblong Liqui-Gels® to the brown oval Liqui-Gels®.

It is important to understand that showing Drug A (green oblong Liqui-Gels®) is bioequivalent to Drug B (ibuprofen suspension) and Drug B (ibuprofen suspension) is bioequivalent to Drug C (brown oval Liqui-Gels®), in separate studies, does not prove that Drug A (green oblong Liqui-Gels®) is bioequivalent to Drug C (brown oval Liqui-Gels®). In this situation, the bioequivalence of Drug A to Drug C can be evaluated by a clinical bioequivalence study comparing Drug A to Drug C and/or by dissolution testing. The Agency determines which studies are necessary on a case by case basis. The significance of the differences in the formulations of the two products is pivotal in this assessment.

In our preliminary review of your application, we noticed that all clinical trials were conducted using the green oblong product, not the brown oval product which you intend to market. Although both the green oblong and brown oval products were tested against the same reference product (i.e., ibuprofen suspension), we have determined that a direct comparison of the brown oval and the green oblong products is necessary. Given the formulation change being made and the magnitude of the change, in vitro dissolution testing should be sufficient to detect the presence or absence of a significant change in in vivo behavior. Accordingly, we recommend the following:

> Consistent with agency guidance, you should conduct in vitro dissolution testing using both the green and the brown Liqui-Gels® products using the approved dissolution media and apparatus described in your original dissolution testing protocol. Please provide individual capsule dissolution profiles over the first 30 minutes using the following timepoints, 0, 5, 10, 15, 20, 25, and 30 minutes. These dissolution profiles should be compared by difference factor (f_1) and similarity factor (f_2). Testing parameters are described in the Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms (Aug. 1997), which may be accessed on the world wide web at the address http://www.fda.gov/cder/guidance.htm. If the dissolution testing described in the guidance fails to support bioequivalence, additional bioequivalence testing may be required.

Furthermore, the language in the cover letter to your supplemental NDA describes the brown oval Liqui-Gels® as a new drug product. It is unclear whether you intend to market the brown oval product as Advil Migraine, while continuing to market the green oblong product as Advil Liqui-Gels®. We request that you provide clarification on this issue. Absent clarification, we will assume this is the strategy you intend to follow.

These comments are being provided to you to give you notice of preliminary issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so.

If you have any questions regarding this application, or the dissolution testing needed to complete this application, please contact Kerry Rothschild, Esq., Regulatory Project Manager, at 301-827-2284.

Sincerely yours,

/S/

Charles J. Ganley, M.D.
Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

ORIGINAL

NC

SE 1-[illegible]

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

July 7, 1999

NDA 20-402, S-005
Advil® Liqui-Gels®
(Ibuprofen, 200 mg)
Supplement for Migraine Headache Indication

General Correspondence: Advil Migraine Data Set Diskettes
(Submitted May 14, 1999 - Additional Review Copy)

Armando Oliva M.D. (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Oliva,

Please refer to the Supplemental New Drug Application for Advil® Migraine submitted May 14, 1999, and sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins"), a division of American Home Products Corporation.

Three diskettes containing Data Sets in SAS transport format for clinical studies AM-98-01, AM-98-02 and bio-study PV-96-08 were included in Section 10, Volume 51 page10-7739 of the sNDA. As requested an additional copy of all three diskettes are provided for review.

The CD-ROM included with volume 1 of the sNDA submission and provided directly to you on June 21, 1999 contains the Annotated CRF and Data Set documentation for clinical studies AM-98-01 and AM-98-02.

If you have any questions regarding this information, please contact the undersigned at (973) 660-6031 or Mary Davis at (973) 660-5825.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Hulon W. McCain

Hulon W. McCain Ph.D.
Director
Regulatory Affairs/Toxicology

15.1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-402/S-005

MAY 26 1999

Whitehall-Robins Healthcare
5 Giralda Farms
Madison, NJ 07940

Attention: Sharon C. Heddish
Vice President, Regulatory Affairs-Worldwide

Dear Ms. Heddish:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Advil® (ibuprofen, USP) Liqui-Gels

NDA Number: 20-402

Supplement Number: S-005

Date of Supplement: May 14, 1999

Date of Receipt: May 17, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on July 16, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Over-the-Counter Drug Products, HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Maria Rossana R. Cook, M.B.A.
Chief, Project Management Staff
Division of Over-the-Counter Drug Products, HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research

USER FEE COVER SHEET/VALIDATION FORM

DA # 20-402 DOCUMENT ID/LETTER DATE MAY 14, 1998 SE1-005

PPLICANT NAME

RODUCT NAME PROVEL (IBUPROFEN) 200 MG SOFT GEL CAPSULE

FORM MUST BE COMPLETED ASAP

YES User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COMIS DATA ELEMENTS

YES NO CLINICAL DATA?
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. "Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?

YES NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION		
N_____	_____	FEE	NO FEE
N_____	_____	FEE	NO FEE

YES NO BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N_____	_____	N_____	_____

P S PRIORITY OR STANDARD?

CSO SIGNATURE/DATE

/S/

SCSO CONCURRENCE SIGNATURE/DATE

/S/ for 5/19/98

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-402/S-004

Whitehall-Robins Healthcare
Attention: Sharon Heddish
VP Worldwide Regulatory Affairs
5 Giralda Farms
Madison, NJ 07869

Dear Ms. Heddish:

Please refer to your supplemental new drug application dated November 20, 1998, received November 27, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil® (ibuprofen) Liquigels®.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplemental new drug application provides for an in-process pH specification of [redacted] for the liquid fill material prior to encapsulation. Your submission stated November 20, 1998, as the implementation date for the change.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Kerry Rothschild, Project Manager, at (301) 827-2222.

Sincerely,

/S/ 2-9-99

Hasmukh B. Patel, Ph.D.
Chemistry Team Leader
Division of New Drug Chemistry III
Center for Drug Evaluation and Research

ORIGINAL

Noted
4/21/99
K&L

NDA SUPPL AMENDMENT

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

WHITEHALL ROBINS

NDA SUPPL AMENDMENT

S-003-NDA

January 26, 1999

NDA 20-402
Advil® (Ibuprofen) Liqui-Gels®

Amendment to a Pending Supplemental Application (S-003)
Chemistry, Manufacturing and Controls

Debra Bowen, M.D., Director
Division of Over-the-Counter Drug Products (HFD-560)
ATTENTION: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Bowen:

Reference is made to new drug application (NDA) 20-402 sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins") for Advil® (ibuprofen) Liqui-Gels®, specifically to supplement S-003 submitted on September 30, 1998. Supplement S-003 provides for a change in the packaging components to those typically used for the rest of the Advil product line (i.e. tablets, caplets, gel caplets, covered under NDA 18-989), and the addition of a pouch configuration. Additional reference is made to the January 22, 1999 telephone conversation between representatives of Whitehall-Robins and the Division of OTC Drug Products ("the Division") relative to the pending supplement.

The Division requested that Whitehall-Robins withdraw the *Packaging Component Equivalency Protocol* contained in the pending supplement. It was also noted that stability data on pages 123 and 124 [redacted] was identical to data included on pages 127 and 128 [redacted] The Division requested that this error be explained and corrected.

Pursuant to the Division's request, Whitehall-Robins is hereby amending pending supplemental application S-003 as follows:

(1) Whitehall-Robins hereby requests that the *Packaging Component Equivalency Protocol* contained in the original supplement be withdrawn. In accordance with a previous request from the Office of New Drug Chemistry, these types of protocols will be negotiated with the Agency and submitted as separate supplements to all affected NDAs.

(2) The discrepancies noted in the stability report were due to transcription errors, which occurred when the summary tables were created. Specifically, pages 123 and 124 [redacted] have been identified as containing transcription errors; the data contained on pages 127 and 128 [redacted] is correct. The errors have been corrected, and replacements for pages 123 and 124 are enclosed. Whitehall-Robins apologizes for any inconvenience that this issue may have caused. We intend to prevent such occurrences in the future by creating computerized reports through our Laboratory Information Management System (LIMS) that will eliminate the need for data handling.

We trust that this response satisfactorily addresses any outstanding chemistry, manufacturing and controls issues with respect to this supplement. If you have any questions or comments relative to this submission, please feel free to contact the undersigned at (973) 660-6896 [fax: (973) 660-7162].

Whitehall-Robins hereby certifies that a field copy of this submission has been forwarded to the FDA District Offices in North Brunswick, NJ and Buffalo, NY.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

K. Warner

Ken Warner
Associate Director, Regulatory Affairs CMC

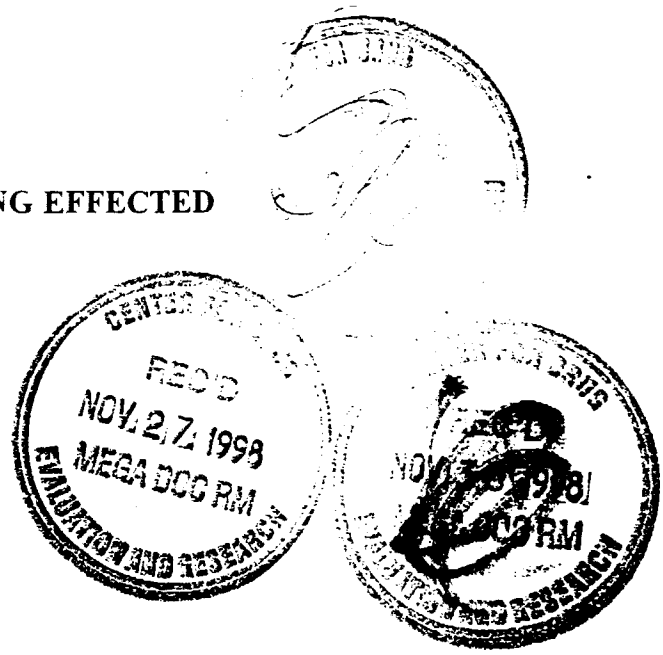
cc: K. Rothschild (HFD-560)

ORIGINAL

20-402 S-004
SCMSCS

Whitehall-Robins
Five Giralda Farms
Madison, NJ 07940-08[illegible]
Telephone (973) 660-[illegible]
Website address: http:[illegible]ealthfront.com

November 20, 1998



NDA 20-402
Advil® (Ibuprofen) Liquigels

SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED
Chemistry, Manufacturing and Controls

Debra Bowen, M.D., Director
Division of OTC Drug Products **(HFD-560)**
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Bowen:

Reference is made to new drug application (NDA) 20-402 sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins") for Advil® (ibuprofen) liquigels. This NDA was originally sponsored by Sandoz Pharmaceuticals Corporation ("Sandoz"), and was transferred to Whitehall-Robins on April 22, 1996. The subject drug product consists of a liquid core, containing 200 mg of ibuprofen, encapsulated in a soft gelatin shell. The liquigels are manufactured by R.P. Scherer, North America ("R.P. Scherer") at their St. Petersburg, FL facility, and are shipped in bulk to Wyeth-Ayerst's Rouses Point, NY facility for packaging and final release.

During the review of the subject NDA, FDA requested the incorporation of an in-process specification for the pH of the liquid fill material prior to encapsulation. In the NDA amendment dated February 14, 1995 (response #2, pg. 7) Sandoz responded that R.P. Scherer would monitor the fill solution pH as an [redacted] and that after the first [redacted] commercial batches had been manufactured and tested, an in-process specification would be negotiated with FDA.

Whitehall-Robins Healthcare **NDA 20-402**
Supplemental Application: In-Process pH Specification **Advil® Liquigels**
November 20, 1998

In fulfillment of this post-approval commitment, Whitehall-Robins is hereby submitting this supplemental application providing for an [redacted] specification of [redacted] for the liquid fill material prior to encapsulation. Although pH testing of the fill material has been conducted routinely on batches of the subject drug product, results have only been recorded; there is currently no specification. Consequently, this supplement is being submitted in accordance with 21CFR 314.70(c)(1) to provide for the addition of "a new specification....., or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, and purity which it purports or is represented to possess."

Enclosed is a report that contains a tabulation and analysis of the [redacted] results for [redacted] batches of Advil Liquigels. The report also contains a copy of the test method used to determine the pH of the fill material. Please note that this method is the same as the NDA-approved method used to monitor the pH of the filled liquigels (on stability). [redacted] will be implemented immediately, and the batch production records for the subject drug product will be updated accordingly.

If you have any questions or comments, please feel free to contact the undersigned at (973) 660-6896 [fax (973) 660-7162]. Thank you for your prompt review of this supplemental application.

Whitehall-Robins hereby certifies that a copy of this submission has been forwarded to the FDA District Offices in North Brunswick, NJ and Buffalo, NY.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Ken Warner
Associate Director, Regulatory Affairs

cc: S. Cook (HFD-550)
S. Mason (HFD-560)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-402/S-003

OCT 8 1998

Whitehall-Robins Healthcare
5 Giralda Frams
Madison, New Jersey 07940

Attention: Sharon Heddish, VP Worldwide Regulatory Affairs

Dear Ms. Heddish:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Advil® (ibuprofen) Liquigels

NDA Number: 20-402

Supplement Number: S-003

Date of Supplement: September 30, 1998

Date of Receipt: October 5, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on December 4, 1998, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Over-the-Counter Drug Products, HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

For Maria Rossana R. Cook, M.B.A.
Chief, Project Management Staff
Division of Over-the-Counter Drug Products, HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research

SUPPL

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

WHITEHALL ROBINS

NDA NO. [redacted] REF. NO. [redacted]

NDA SUPPL FOR [redacted]

ORIGINAL

September 30, 1998

NDA 20-402
Advil® (ibuprofen) Liquigels

Supplemental Application - Packaging Changes

Debra Bowen, M.D., Director
Division of OTC Drug Products **(HFD-560)**
Center for Drug Evaluation and Research **V**
Food and Drug Administration
ATTENTION: Document Control Room
9201 Corporate Blvd.
Rockville, MD 20857

Dear Dr. Bowen:

Reference is made to new drug application (NDA) 20-402 sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins") for Advil® (ibuprofen) liquigels. This NDA was originally sponsored by Sandoz Pharmaceuticals Corporation ("Sandoz"), and was transferred to Whitehall-Robins on April 22, 1996. The subject drug product consists of a liquid core, containing 200 mg of ibuprofen, encapsulated in a soft gelatin shell.

NDA 20-402 provides for the subject drug product to be packaged in bottles and blisters; the approved packaging components represent those intended for use by Sandoz. **Whitehall-Robins is hereby submitting this supplemental application to provide for a change from the current "Sandoz" packaging components, to those typically used for the rest of the adult Advil product line (tablets, caplets, gel caplets covered under NDA 18-989); please note that the referenced changes include the addition of a pouch configuration.** The enclosed supplemental application includes a chemistry, manufacturing and controls (CMC) section, and updated labeling representative of the new packaging.

Whitehall-Robins Healthcare **NDA 20-402**
Supplemental Application - Packaging Changes **Advil® Liquigels**
September 30, 1998

Please refer to the attached table of contents for specific information included in this submission. If you have any questions, please feel free to contact the undersigned at (973) 660-5753 [telefax (973) 660-7187] or Hulon McCain at (973) 660-6031. Thank you for your prompt review of this supplemental application.

Whitehall-Robins hereby certifies that a copy of this submission has been forwarded to the FDA District Offices in North Brunswick, NJ and Buffalo, NY.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Hulon W McCain

Sharon Heddish,
Vice President
Worldwide Regulatory Affairs

cc: S. Cook (HFD-550)
S. Mason (HFD-560)

Original

SUPPL NEW CORRESP
ORIGINAL

Whitehall-Robins
Five Giralda Farms
Madison, NJ 07940-0874
Telephone (973) 660-5500
Website address: http://www.healthfront.com

January 13, 1998

NDA 20-402:S-002
Provel Soft Gelatin Capsules (solubilized ibuprofen 200 mg)

Debra Bowen, MD, Director
Division of OTC Drug Products (HFD 560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

General Correspondence Re Supplement 002: Response to FDA Request for Information

Dear Dr. Bowen:

Please refer to NDA 20-402 for Provel, solubilized ibuprofen soft gelatin capsules (200 mg), approved for over-the-counter use on April 20, 1995. Specific reference is made to Supplement 002 submitted December 10, 1996 and subsequent correspondence to S-002 of July 21, 1997 (amendment), and December 15, 1997 (fax) (Attachment 1).

As requested by Ms. Stephanie Mason of the division on January 8, 1998, this letter provides official confirmation of the information faxed to the division on December 15, 1997 regarding package for Advil Liquigels. Attached is a tabular display (attachment 2) of the following information regarding the packaging components for Advil Liquigels: 1) components approved in NDA 20-402, 2) components submitted in supplement 002 and 3) requested amendments. As you can see from the table, the bottle counts in the original NDA were 20, 40 and 80. When we submitted supplement 002, the capsule counts for the bottles were changed in the labeling to 24, 50 and 100. We have decided to revise those counts to conform to the sizes in the original NDA, i.e., 20, 40 and 80. Final printed labeling submitted for this supplement will reflect this change.

The original NDA provided for a blister cavity that contained one capsule. The counts submitted in the original NDA for blister packaging were for cards of 2, 4, 6 and 10 capsules. Carton for blister packages were included in the NDA for 2s and 6s. In responding to the agency on December 12, 1994 regarding blister packaging, Sandoz included the statement " other configurations may be possible in the future since the unit cavity for the blister would be the same". We are requesting to amend supplement 002 to include labeling for the blister card of 4 capsules, the accompanying "traditional" cartoon and a package insert. The insert is identical to that packed with the bottles. We are withdrawing the 2s and 4s matchbook which was submitted in supplement 002. Draft labeling for the 4s blister back, carton and insert are attached herewith (Attachment 3).

Please note the packaging materials we are using are as approved in NDA 20-402. For your reference, we have attached a description of the packaging components from the original NDA (Vol. 3, p. 220)(Attachment 4). We have also attached information on the blister cards which was provided by Sandoz on December 12, 1994 at the request of FDA in their letter of December 9, 1994 (Attachment 5).

If you have comments or questions regarding this information, please contact the undersigned at (973) 660-5753 or in my absence Ms. Mary Davis at (973) 660-5825.

Sincerely,

Mary H Davis for

Sharon Heddish
Vice President
Regulatory Affairs, Worldwide

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-402/SCM-001

OCT 6 1997

Whitehall-Robins Healthcare
Attention: Sharon Heddish
Director, Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Ms. Heddish:

Please refer to your November 11, 1996, supplemental new drug application, received November 13, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Provel(R) (Ibuprofen Liquigels), 200 mg. Please also refer to our letter dated May 2, 1997.

We also acknowledge your submission dated May 30, 1997.

This supplemental application provides for an alternate packaging and testing site and modifications to the stability testing program.

We have completed the review of this supplemental application and it is approved effective as of the date of this letter.

This approval affects only the changes specifically submitted in this supplemental application. Other changes that may have been approved or are pending evaluation are not affected.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have nay questions, please contact Stephanie Mason, Project Manager, for the Division of Over the Counter Drug Products, (301) 827-2275.

Sincerely yours,

/S/ 10-3-97

Hasmukh B. Patel, Ph.D.
Chemistry Team Leader
Division of New Drug Chemistry III
Center for Drug Evaluation and Research

10/24/97 Noted. Info has been relayed to Bio/Pharm. Reviewer. NAI ed. Pharmacist

Whitehall-Robins
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Telephone (201) 660-5500

September 10, 1997

NDA 20-402/S-002
Amendment to Pending Supplemental Application S-002

Debra Bowen, M.D., Director
Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Bowen:

Reference is made to NDA 20-402 for Provel Soft Gelatin Capsule (solubilized ibuprofen 200 mg) sponsored by Whitehall-Robins Healthcare, ("Whitehall-Robins") a division of American Home Products Corporation. Specific reference is made to S-002 (submitted December 10, 1996) which supports a product name change as well as labeling revisions and to an FDA request for information (received via fax on September 8, 1997).

As requested by the agency, we are providing the following 4 graphs (spaghetti plots):

All subjects Advil Liquigel 400 mg - fasted
All subjects Advil Liquigel 400 mg - fed
All subjects Nuprin 400 mg - fasted
All subjects ibuprofen suspension 400 mg - fasted

Please note that statistical analyses were performed using data from a total of 29 subjects, although only 27 subjects completed all 4 phases of the study. Valid data for treatment comparisons was extracted from the 2 subjects that did not finish all 4 phases as both of the subjects completed more than 1 treatment period: 1 subject completed 2 phases of the study; the other subject completed 3 phases. Therefore, 28 subjects are included in the spaghetti plots of Treatments A (liquigel-fasted), B (liquigel-fed) and D (suspension-fasted), and 29 subjects are included in the spaghetti plot of Treatment C (Nuprin-fasted).

It is our understanding that this is the only outstanding information needed for completion of the bioequivalence review by the agency. We look forward to obtaining further feedback on the status of Supplement S-002 after your September 12th review meeting.

If have any questions or comments, please contact the undersigned at (973) 660-5753 or Ms. Mary Davis at (973) 660-5825.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Mary H Davis for

Sharon Heddish
Senior Director, Regulatory Affairs

cc: Desk Copy
Stephanie Mason
Project Manager

APPEARS THIS WAY
ON ORIGINAL

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NDA SUPPL AMENDMENT

ORIGINAL

Whitehall-Robins
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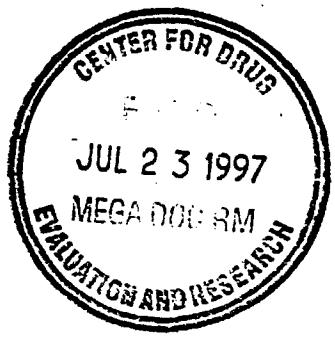
WHITEHALL ROBINS

July 21, 1997



NDA 20-402
Provel Soft Gelatin Capsules (solubilized ibuprofen 200 mg)

SUPPLEMENTAL APPLICATION: AMENDMENT TO S-002

Debra Bowen, MD, Director
Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Bowen:

Please refer to NDA 20-402 for Provel, solubilized ibuprofen soft gelatin capsules (200 mg), approved for over-the-counter use on April 20, 1995. Specific reference is made to Supplement 002 submitted on December 10, 1996, to provide for the following revisions to the approved labeling:

- removal of the "take with food" direction
- modification of the Provel labeling to be consistent with Advil labeling
- conversion to "drug facts" style labeling

In a phone conversation of July 9, 1997, Ms. Rosemary Cook of your division advised Ms. Mary Davis of Whitehall-Robins that a team meeting to determine the status of the review for Supplement 002 will be scheduled. During this phone conversation Ms.Davis indicated we would like to submit a revised principal display panel for the proposed Advil Liquigel packaging. It was agreed we should submit the revised labeling prior to the Divisions' team meeting.

Accordingly, submitted herewith is an amendment to S-002 providing for revised graphics for the principal display panel. Only the sell copy on the principal display panel has changed. Draft labeling for all sizes and packaging configurations are included herein. Please note this is the only amendment to this pending supplement.

For your reference, Whitehall-Robins' minutes of the April 10, 1996 meeting with the Agency to discuss the requirements to remove the "take with food" direction from the approved labeling are attached. As per agreement with the Agency, Whitehall-Robins conducted and submitted (in S-002) a biostudy (PV-96-02) which established the

bioequivalence of Advil Liquigels to ibuprofen suspension. It is our understanding that review of that study by the Agency has been completed.

We hope that we can resolve issues, if any, related to format changes in the labeling as expeditiously as possible so that we can look forward to receiving an action letter in the near future. If you have comments or questions regarding this submission, please contact the undersigned at (201) 66-5753, or in my absence Ms. Mary Davis at (201) 660-5825.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Sharon Heddish

Sharon Heddish,
Director, Regulatory Affairs

ORIGINAL

WHITEHALL ROBINS

Whitehall-Robins
Five Giralda Farms
Madison, NJ 07940-0871
Tel. (201) 660-5500

NDA SUPPL AMENDMENT
S-001

May 30, 1997

NDA 20-402
IBUPROFEN LIQUIGELS (200 MG)

AMENDMENT TO A PENDING SUPPLEMENTAL APPLICATION (SCM-001)
Chemistry, Manufacturing and Controls

Debra Bowen, M.D., Director
Division of Over-the Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

ATTENTION: Document Control Room

Dear Dr. Bowen:

Reference is made to new drug application (NDA) 20-402 sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins") for ibuprofen liquigels, specifically to supplement SCM-001 submitted on November 11, 1996. Supplement SCM-001 provides for Wyeth-Ayerst's Rouses Point, NY facility as an alternate packaging and testing site for the subject drug product. This supplement also provides for slight modifications to the stability testing program, specifically with respect to the storage conditions. Additional reference is made to the approvable letter dated May 2, 1997 (attached), which contained several comments from the Division of Over-the-Counter Drug Products ("the Division") relative to the pending supplement. Enclosed herein, are Whitehall-Robins' responses to the comments contained in the May 2, 1997 letter. Please refer to the table of contents for specific information included in this submission.

Thank you for your prompt attention to this submission. If you have any questions or comments, please feel free to contact the undersigned at (201) 660-6160 [fax: (201) 660-6048].

Whitehall-Robins hereby certifies that a field copy of this submission has been forwarded to the FDA District Offices in North Brunswick, NJ and Buffalo, NY.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Vin Milano
Director, Regulatory Affairs

cc: S. Mason (HFD-560)

ORIGINAL

Whitehall-Robins
5 Giralda Farms
Madison, NJ 07940-0871
Telephone (201) 660-5500

WHITEHALL ROBINS

20402-REF. NO. S-001
Manufacturing

November 11, 1996

NDA 20-402
IBUPROFEN LIQUIGELS (200 MG)

SUPPLEMENTAL APPLICATION
Chemistry, Manufacturing and Controls

Wiley Chambers, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550)
ATTENTION: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Chambers:

Reference is made to new drug application (NDA) 20-402 sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins") for ibuprofen liquigels. This NDA was originally sponsored by Sandoz Pharmaceuticals Corporation ("Sandoz"), and was transferred to Whitehall-Robins on April 22, 1996. The subject drug product consists of a liquid core, containing 200 mg of ibuprofen, encapsulated in a soft gelatin shell.

NDA 20-402 provides for manufacturing operations to be conducted at [redacted] facility. Packaging and testing are approved at the Sandoz facility in [redacted] **Whitehall-Robins is hereby submitting this supplemental application to provide for Wyeth-Ayerst's Rouses Point, NY facility as an alternate packaging and testing site. This supplement also provides for slight modifications to the stability testing program, specifically with respect to the storage conditions.** Please note that Wyeth-Ayerst and Whitehall-Robins are sister divisions of American Home Products Corporation which have consolidated Operations and Quality Assurance functions. Certain research (accelerated) stability testing will also now be conducted at Whitehall-Robins' research facilities in Hammonton, NJ and Richmond, VA. Please refer to the attached facility listing for specific information relative to the site names and addresses.

It should be noted that the Rouses Point facility currently manufactures, packages and tests numerous prescription and over-the-counter products. They also currently manufacture, package and test several ibuprofen-containing NDA products for Whitehall-Robins including Advil (ibuprofen) Tablets and Caplets and Advil Cold & Sinus (ibuprofen / pseudoephedrine HCl) Tablets and Caplets. The subject liquigel product is approved for packaging in standard high density Please note that the are now tested in accordance with the requirements of USP <661>. The Rouses Point facility is equipped to package these configurations and will utilize the NDA approved packaging components.

In support of this submission, Whitehall-Robins commits to place the first three (3) commercial batches of ibuprofen liquigels packaged at the Rouses Point facility into the stability program in each of the two different packaging configurations). These batches will be stored and tested in accordance with the attached stability conditions and test intervals. Please note that there are slight modifications to the currently approved stability storage conditions for the subject drug product which are described in the attached comparative listing. The proposed storage conditions have been modified to conform to those specified in the International Conference on Harmonization (ICH) guidelines. Subsequent to commercial distribution of packaged product from the Rouses point facility, at least batch will be entered into the packaged product stability program on annual basis and will be tested at yearly intervals. Whitehall-Robins / Wyeth-Ayerst will also utilize the product specifications and analytical test methods approved in NDA 20-402 and will perform all appropriate analytical method transfer work. The expiration period will be unaffected by the proposed change in packaging facility.

Based on the overall experience of the Rouses Point facility, specifically with respect to ibuprofen-containing products, this facility is well-equipped to handle the proposed packaging and testing operations for the ibuprofen liquigel product.

Thank you for your prompt attention to this submission. If you have any questions or comments, please feel free to contact the undersigned at (201) 660-6160 [fax: (201) 660-6048].

Whitehall-Robins hereby certifies that a field copy of this submission has been forwarded to the FDA District Offices in North Brunswick, NJ and Buffalo, NY.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE

Vin Milano
Director, Regulatory Affairs

cc: Sandra Cook (HFD-550)