

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-393 & 21-394

APPROVAL LETTER(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-393
NDA 21-394

Wyeth Consumer Healthcare
Attention: Sharon C. Heddish
Vice President, Global Regulatory Affairs
Five Giralda Farms
Madison, NJ 07940

Dear Ms. Heddish:

Please refer to your new drug applications (NDA) dated October 16, 2001, received October 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil PM Liqui-Gels (200 mg ibuprofen/25 mg diphenhydramine HCl capsules) and Advil PM Caplets (200 mg ibuprofen/38 mg diphenhydramine citrate tablets).

We acknowledge receipt of your submissions dated December 6, 2001; January 7, 11 and 24, February 15, March 11 and 19, May 8, 17, and 23, July 9, August 15, 19 and 29 (2 submissions), September 9 and 13, and December 10, 2002; February 5, April 23, May 29, June 30, November 20, and December 23, 2003; January 5 and 20, February 25 (2 submissions), March 5, May 6 and 14, and September 23, 2004; June 27, July 19, August 10, and 31, September 16, November 17, December 13 and 14, 2005.

The June 27, 2005 submission constituted a complete response to our December 18, 2003 action letter.

These new drug applications provide for the use of Advil PM Liqui-Gels and Caplets for relief of occasional sleeplessness when associated with minor aches and pains.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted representative labeling (blister pack and carton labels for NDA 21-393 and immediate container and carton labels for NDA 21-394 submitted December 13, 2005; 4-count gravity feed dispenser and shelf tray labels for NDA 21-393 and 2-count professional pouch dispenser label for NDA 21-394 submitted December 14, 2005), and must be in the "Drug Facts" format (21 CFR 201.66). **FPL must be submitted for all marketing SKUs, identical to the representative labeling, except for declaration of net quantity of contents statement to reflect the package size, submitted December 13, 2005.** Marketing the products with FPL that is not identical to the approved labeling text and in the required format may render the products misbranded and unapproved new drugs.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15

of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions “**FPL for approved NDA 21-393**” or “**FPL for approved NDA 21-394**”, respectively. Approval of these submissions by FDA is not required before the labeling is used.

We remind you to remove the “NEW” flag from the Principal Display Panel after 12 months of OTC marketing.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the waiver granted on October 11, 2001 for the pediatric study requirement for the age range of birth to less than 12 years of age for these applications.

In addition, we request that you submit two copies of the introductory promotional materials you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Neel Patel, Regulatory Project Manager at (301) 796-0970.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Office of Nonprescription Products
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure

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

/s/

Charles Ganley
12/21/2005 10:01:42 AM

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APPROVABLE LETTER(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-393

Wyeth Consumer Healthcare
Attention: Ms. Sharon C. Heddish
Vice President, Regulatory Affairs
Five Giralda Farms
Madison, NJ 07940-0871

Dear Ms. Heddish:

Please refer to your new drug application (NDA) dated October 16, 2001, received October 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil[®] PM (ibuprofen, 200 mg/ diphenhydramine hydrochloride, 25 mg) Liquigels.

We acknowledge receipt of your submissions dated December 6, 2001; January 7, 11 (2) and 24, February 15, March 19, May 8, 17 and 23, July 9, August 15, 19 and 29 (2), September 9 and 13, December 10, 2002; February 5, April 23, May 29, June 30 and November 20, 2003.

We also refer to your April 23, 2003, request for formal dispute resolution received on April 24, 2003. The appeal concerned the approvable letter dated August 8, 2002, issued by the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products and the Division of Over-the-Counter Drug Products. Prior appeals of this decision were made to the Office of Drug Evaluation V and the Office of New Drugs, and were denied in decisions dated January 10, and February 26, 2003, respectively.

At your request, a meeting with the Center Director was held on May 20, 2003, to discuss your appeal of this decision. During that meeting, you presented new analyses of data from your clinical investigations that had not previously been submitted for review by FDA. In a subsequent teleconference on June 13, 2003 with you, Dr. Roger Berlin, Dr. John Jenkins and Ms. Kim Colangelo, you were advised to submit these new analyses for our review as part of a complete response to the August 8, 2002 approvable letter.

Your submission dated June 30, 2003 contained these new analyses of the NDA data and constituted your complete response. This resubmission purported to address all of the deficiencies specified in our August 08, 2002 approvable letter.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies:

CLINICAL:

The reanalyses of data from studies AE 98-01 and AE 98-02 do not adequately support the efficacy of this product for the proposed indication. These studies were flawed by design with regard to their ability to provide an unbiased determination of the effect, if any, of the combination product versus ibuprofen alone on the endpoint of sleep duration. These studies were specifically designed to assess sleep latency as a primary endpoint and sleep duration was one of numerous secondary, supportive, endpoints that were to be assessed. We remain concerned that the forced awakenings at the time when the diphenhydramine component of the combination would be expected to be at or near its maximum effect may have introduced a bias in favor of the combination product with regard to assessment of sleep duration. This concern is relevant to the interpretation of these studies with regard to efficacy of the combination product since in actual use consumers would not

experience forced awakenings at regular intervals. It remains unproven whether the combination product would result in an enhanced duration of sleep under such conditions and the subgroup analyses you submitted do not adequately address the concerns.

Subgroup Reanalyses Submitted:

Your subgroup reanalyses of trials AE 98-01 and AE 98-02, which attempted to address our concerns regarding the forced awakening of subjects for pain assessment and its potential impact on the endpoint of sleep duration, do not adequately answer our concerns about the interpretation of the data for the sleep duration endpoint. Specifically, these reanalyses do not adequately support your assertion that awakening of subjects had no meaningful impact on the sleep duration endpoint in these studies for the following reasons:

- a) There are numerous subgroups that could be chosen for reanalysis. It is not clear why the subgroup you chose should take precedence over others.
- b) Given that the first awakening by the investigator occurred at 90 minutes, there is no explanation provided to support your selection of the subgroup asleep and awakened at 120 minutes as the appropriate one for reanalysis.
- c) Your reanalyses fail to account for subjects who were awakened at 90 minutes and were unable to get back to sleep by 120 minutes. Furthermore, the subgroup you selected for reanalysis accounts for only approximately 50% of the subjects randomized in study AE 98-01 and only approximately 70% in study AE 98-02. When we analyzed the subgroup of subjects asleep and awakened at 90 minutes in study AE 98-02, we found that 18% more in the combination group were able to get back to sleep by 120 minutes. This difference in the percentage of subjects able to get back to sleep reinforces our concerns about the impact of waking on the duration of sleep. The 90 minute analysis suggests that there is a differential effect between the treatment groups and that the subgroup chosen for reanalysis may influence the results.
- d) The reanalysis of sleep duration for those subjects asleep at 150 minutes was based on a partial dataset and may not be representative of the population of interest. In addition, this assessment for sleep duration may be influenced by both the awakening effect and the drug effect. It is difficult to dissect the awakening effect from any drug effect based on these analyses. This awakening may reflect the particular pharmacokinetics of diphenhydramine (DPH), allowing more patients in this treatment arm to fall back to sleep, which may then artificially lengthen the apparent duration of sleep in those receiving DPH.

Other Information Submitted:

In your overview of the June 30, 2003 submission, you suggest that it is common in sleep studies to create conditions such as waking that make sleep more difficult. You also note that a survey by the National Sleep Foundation found that 65% of subjects with nocturnal sleep problems and pain reported middle of the night awakenings. You suggest that the survey data support awakening of subjects in a sleep efficacy study that enrolls subjects with pain. Because every subject in a study may not naturally awaken during the night, it seems counter intuitive that the design of a sleep study in a population with pain would include forced awakenings if the primary endpoint is sleep duration.

When evaluating a combination analgesic-sleep aid drug product, forced awakening of subjects may answer the question of whether a sleep aid is a sleep aid but it does not answer the question of whether it contributes to the effect of the combination. This may be relevant in this instance because of the effectiveness of single ingredient ibuprofen on the sleep latency endpoint.

We find this information does not support forced awakenings in a sleep study, especially if the primary measure of efficacy is sleep duration. There is a paucity of data in the medical literature on the effect of sleep on pain threshold, the effect of pain on the stages of sleep and the effect of pain relievers on pain threshold and stages of sleep. Throughout the review of this application, your submissions to address some of these issues have been limited to the anecdotal experience of your expert consultant and have not contained scientifically substantive data.

INFORMATION NEEDED TO RESOLVE DEFICIENCIES:

We remind you that during the OTC Drug Monograph review, the Advisory Review Panel on OTC Sedative, Tranquilizer and Sleep Aid Drug Products set a high standard with regard to the type of data needed to support a combination analgesic sleep aid product. The Panel was concerned about a proliferation of combination sleep-aid products for conditions that may impair sleep. The Panel noted pain may indeed prevent sleep, as might acid indigestion, coughing, or sunburn. They noted that if they were to follow the rationale that pain discomfort prevents sleep, and that something which affords relief from pain discomfort can therefore be considered a night-time sleep aid, it would be necessary to permit the use of a similar nighttime sleep claim for any ingredient used to treat any condition that might interfere with sleep. Such ingredients might be antacids, cough remedies, or sunburn lotions. Nighttime sleep-aid labeling claims made on the basis of analgesics alone would be misleading. The Panel recommended that for combinations containing both antihistamines and analgesics, studies are required to show that there is a target population requiring ingredients concurrently for both pain and sleep. They recommended using a factorial design testing the combination against each ingredient and placebo to establish the contribution of each ingredient. In the proposed and final rule, the FDA concurred with these recommendations of the Panel.

We do not find that your studies reach the level of evidence expected by the Panel. When the panel recommended that it was necessary to identify a population who would benefit from the combination, demonstrating the contribution of each ingredient would help establish that a population existed. Because ibuprofen was very effective compared to the combination for many of the sleep endpoints, it is not clear from the data submitted that a population of benefit encompassing both pain and sleep disorder has been identified. Consequently, it is important to clearly establish the contribution of each ingredient in the study where the results can be extrapolated to other relevant OTC populations. Based on results from your past studies using the dental pain model, you may want to consider an alternative population that may better reflect the contributions of the individual components.

To establish adequate evidence of an effect of DPH in the combination on sleep duration, an additional trial is needed. This trial should be designed to determine the contribution of the components with sleep duration as the primary endpoint and no artificial awakenings as occurred in studies AE 98-01 and AE 98-02. Clinically significant results from this study supporting your proposed indication, in addition to data presented in the original NDA, would be sufficient for approval. Although not addressed in your submission, there is concern that DPH may adversely impact the analgesic characteristics of ibuprofen. Therefore, sleep latency which can be viewed as a surrogate for pain relief, needs to also demonstrate a treatment response consistent to that for sleep duration. We recommend that you meet with the Divisions to discuss the protocol design before proceeding.

OTHER RECOMMENDATIONS:

BIOPHARMACEUTICS:

We also ask that you consider the issues listed below:

1. Based on the dissolution study data, the dissolution method using Apparatus USP I (Basket) in phosphate buffer, 200 mM, pH 7.2 is acceptable. Using a rotational speed of 150 rpm is acceptable as

an interim method provided that you submit the dissolution testing results for old samples at a rotational speed of 100 rpm.

2. Your proposed dissolution specification of $Q = \text{---}$ at 45 minutes is not acceptable. We recommend an interim specification of $Q = \text{---}$ at 45 minutes for both active components—ibuprofen and diphenhydramine HCl— until more data is available on stability of the test product to support a different dissolution specification.

LABELING:

A full review of the labeling will not be undertaken until you have submitted information to support the efficacy of ibuprofen 200 mg and diphenhydramine hydrochloride 25 mg in a fixed combination oral liquid-filled capsule.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

NDA 21-393

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The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 301 827-2090.

Sincerely,

{See appended electronic signature page}

Jonca C. Bull, M.D.

Director

Office of Drug Evaluation V

Center for Drug Evaluation and Research

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

/s/

Jonca Bull
12/18/03 04:03:03 PM



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Rockville MD 20857

NDA 21-393

Wyeth Consumer Healthcare
Attention: Ms. Sharon C. Heddish
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Please refer to your new drug application (NDA) dated October 16, 2001, received October 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil PM (ibuprofen/diphenhydramine hydrochloride) Liquigels.

We acknowledge receipt of your submissions dated December 6, 2001, and January 7 and 11, March 19, and May 8, 2002.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

CLINICAL:

1. Study 98-02, the pivotal study in your drug development program, does not adequately support the efficacy of this product for the proposed indication. There are inconsistencies in the results of the primary sleep endpoints, sleep latency (cumulative percent asleep at 60 minutes) and sleep duration. For sleep latency, ibuprofen is numerically superior to ibuprofen/diphenhydramine. This difference almost achieves statistical significance ($p = 0.1$). For sleep duration, ibuprofen/diphenhydramine is superior to ibuprofen. In attempting to explain the discrepancy between these results, one cannot rule out the possibility that awakening the subjects at 90 and 120 minutes after ingestion of medication had a negative impact on the measure of sleep duration. The effect of diphenhydramine in the combination product may only be realized under these conditions. There are no other sleep endpoints to support the contribution of diphenhydramine to the combination product. Consequently, the benefit of diphenhydramine in the combination product has not been established.

You should conduct another study evaluating sleep duration and sleep latency using methodology that will not bias the outcome of either endpoint. The data from this study should also establish a consistent result between the sleep endpoints. If you are able to conduct a single study that adequately establishes the benefit of the individual components to the combination product, the clinical information in the current application would suffice as supportive data. The protocol design should be discussed

with the Agency before proceeding.

7 Study 98-04

CHEMISTRY:

3. The proposed specification for the drug product does not appear to be adequate to preserve the identity, strength, quality, purity, stability and bioavailability of the drug. Specific comments concerning proposed acceptance criteria for specified degradation products, the absence of acceptance criteria for unspecified degradation products, and the proposed analytical procedure and acceptance criteria for the dissolution test were communicated on August 7, 2002. Please revise the specification or provide justification for the proposed tests and acceptance criteria, as appropriate.
4. Please provide confirmation that the gelatin used in the drug will be free of risks associated with human exposure to BSE (bovine spongiform encephalopathy) affected materials.

BIOPHARMACEUTICS:

5. The dissolution results submitted using the proposed dissolution method demonstrates that for the product formulation evaluated, > 90% of ibuprofen and diphenhydramine citrate were dissolved in 10 minutes. This dissolution rate appears too rapid to allow for maximum discriminating power to detect products with poor in vivo performance. Please provide scientific data on the dissolution method development in terms of the different mediums and conditions tested support to the selection of the proposed dissolution method.

LABELING:

6. A full review of the labeling will not be undertaken until you have submitted information to support the efficacy of ibuprofen 400 mg and diphenhydramine hydrochloride 50 mg in a fixed combination oral liquid-filled capsule in relieving occasional sleeplessness when associated with — minor aches and pain.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include

data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
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 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

NDA 21-393

Page 4

If you have any questions, please contact Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

{See appended electronic signature page}
Charles Ganley, M.D.
Division Director
Division of Over-The-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

{See appended electronic signature page}
Lee S. Simon, M.D.
Division Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Lee Simon
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Charles Ganley
8/8/02 05:01:42 PM