of faxes on 8-10-99. The mutually agreed upon final labeling [SONATALABAP6.DOC] is included with the approval letter.

Dr. Paul Andreason reviewed the 10-22-98 safety update.

2.0 SAFETY UPDATE

The safety update included reports of serious adverse events (SAEs), adverse dropouts, and other adverse events for new patients and new information for existing patients. The safety update covered a period from 10-1-96 through 6-30-98 for the non-Japanese studies and from 6-1-97 through 6-30-98 for the Japanese studies. All of the new safety data for non-Japanese patients came from open studies. New safety data from Japanese patients came from short-term controlled trials.

-For the non-Japanese patients, the focus was on SAEs and adverse dropouts; there were no deaths. There were 2 reports of seizure. While neither case can be definitively attributed to zaleplon, they will be noted in labeling. There were 2 reports of modest transaminitis associated with zaleplon treatment that were not otherwise explained. Abnormalities in liver function tests is already noted in "Other Events." There was also a case of vertigo, however, this event already appears in the 1% table. Otherwise, the new safety findings were not noteworthy.

-There was no new pertinent safety information from the Japanese studies.

3.0 WORLD LITERATURE UPDATE

The sponsor's literature update covered the period from Feb, 97', the cut-off date for the original literature review, and Dec, 98.' A listing of titles of 16 published papers and titles of 13 abstracts of presentations were provided in the 2-26-99 response to the approvable letter. Timothy Whitaker, MD, the medical monitor from WA, reviewed these materials and provided a warrant that there were "no findings that would adversely affect the conclusions about the safety of Sonata." I reviewed the titles of these papers and abstracts and saw nothing that was suggestive of new important safety information.

4.0 REGULATORY STATUS UPDATE

The sponsor noted in the 2-26-99 submission that Sonata applications have been filed in 24 nonUS countries. While positive preliminary opinions have been granted in the 15 European countries, final approval has not yet been granted in any country. Thus, there were no approved foreign labels available for review.

5.0 PEDIATRIC STUDY REQUEST

We initially responded to the 3-18-99 request for a Written Request with a 6-7-99 letter indicating that we would be unable to issue a Written Request until we could determine, with the help of the pediatric advisory committee, whether or not it would be appropriate to encourage development of Sonata in pediatric populations. The final approval letter will include standard language provided by the pediatric committee regarding the deferral of pediatric studies until the above determination can be made.

6.0 CHEMISTRY DEFICIENCIES

It is my understanding that all remaining CMC issues have been resolved as of this time, with the exception of an expired EER. It is my impression that this kind of deficiency would not ordinarily be considered sufficient justification for delaying a final approval action. In any case, we will forward the approval package to the Office, noting this deficiency.

7.0 REQUEST FOR PHASE 4

[redacted]

8.0 DISSOLUTION SPECIFICATION

We have reached agreement with the sponsor on a dissolution method and specifications, and these details are included in the approval letter. .

9.0 LABELING/PPI

A major issue in our labeling negotiations involved the question of how best to characterize dose response information for safety and effectiveness. The sponsor's preferred approach was to try to distinguish between the 20 mg dose as a dose that was too risky to justify its marginal advantages over the lower doses, which they considered effective and essentially free of any important risks. We argued against this approach, suggesting rather that there is dose dependency for both safety and efficacy, and further, that the dose may need to be individualized for certain patients in order to achieve the optimal response. Clearly, the plasma concentration actually achieved with any given

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

DF

Food and Drug Administration
Rockville MD 20857

NDA 20-859

Wyeth-Ayerst Laboratories
Attention: Roy J. Baranello Jr.
P.O. Box 8299
Philadelphia, PA 19101

JAN 13 1998

Dear Mr. Baranello:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Sonata (zaleplon) capsules 5 mg and 10 mg

Therapeutic Classification: Standard

Date of Application: December 30, 1997

Date of Receipt: January 6, 1998

Our Reference Number: 20-859

We did not received the appropriate user fee for this application until January 6, 1998. Under section 736(e) of the Prescription Drug User Fee Act of 1992 (PDUFA), an application is considered incomplete and will not be accepted for filing until all fees owed have been paid. Therefore, the receipt date for this submission (which begins the review for fileability) is January 6, 1998.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 7, 1998 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/ [redacted] 1/12/98

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

MEMORANDUM

DATE: August 12, 1999 /S/ [redacted] 8/13 99

FROM: Russell Katz, M.D.

TO: Director
Office of Drug Evaluation I/HFD-100

SUBJECT: Approval Recommendation for NDA 20-859

Wyeth-Ayerst submitted their response to the Agency's 1/6/99 approvable letter on 2/26/99. All reviews of the sponsor's re-submission have been completed, and the review team recommends that the application be approved. In particular, agreement has been reached between the sponsor and review team on labeling. Dr. Laughren has performed an overview of the relevant issues (see his memo of 8/11/99).

The purpose of this memo is to highlight those more important sections in labeling to which the division and sponsor have agreed but that differ from the draft labeling that accompanied the approvable letter. These changes are all relatively minor.

Pharmacokinetics

Race subsection

The label accompanying the approvable letter described an increase in Cmax and AUC in the Japanese population compared to the Caucasion population which was attributed to a likely difference in enzyme activity between the races, and explicitly stated to not be related to differences in weight. The current version of labeling states that the difference is likely due to weight and/or environmental factors, the latter of which may result in differences in enzyme activity. This change is supported by a re-analysis performed by the staff of OCPB.

Clinical Trials

Controlled Trials

The description of a transient insomnia trial in the approvable labeling has been removed because this trial failed to distinguish the effects of a standard hypnotic as well as 2 doses of Sonata from placebo. In addition, there have been some changes in language in this section, including some minor changes in the first paragaraph, and the addition of an introductory paragraph in the Chronic Insomnia: Non-Elderly Patients sub-section.

Studies Pertinent to Safety Concerns of Sedative/Hypnotic Drugs

The approvable labeling stated that reports for larger clinical trials revealed the infrequent occurrence of next-day somnolence. The current version of labeling states that these trials did not suggest such a difference. This latter statement is supported by a re-analysis of these data.

In addition, the approvable labeling stated that there was evidence of dose-dependent worsening of sleep the first night after treatment discontinuation. The current labeling states in more detail the actual responses by dose.

Indications

The wording has been slightly changed and re-ordered.

Precautions

General

A new paragraph, titled Timing of Drug Adminstration has been added, which describes the necessity for patients to take Sonata immediately before bedtime or while in bed, and which describes the potential consequences if the drug is administered while the patient is up and about.

Carcinogenesis, Impairment of Fertility, Pregnancy

The approvable labeling described the multiples of the human exposure (AUC) achieved in the animal studies. The current label describes multiples in terms of dose on a mg/m2 basis. This has been done because it was felt that the exposure data were unreliable.

Adverse Reactions

The table of ADR incidence in controlled trials has been changed to explicitly present the data by dose group (Pbo, 5&10mg, 20 mg) and only those events which occurred with an incidence of at least 1% in the 20 mg group and in which this incidence was greater than placebo, based on discussions held with the firm at our meeting of 8/4/99.

Abuse, Dependence, and Tolerance

Dependence

The description of 2 patients who experienced a seizure has been added, as discussed in the 8/4/99 meeting.

Tolerance

The description of a sleep laboratory study in which latency to persistent sleep was diminished for the first 2 nights only of the 28 day study has been removed because this study was not considered to directly address the question of tolerance. The results of this trial are described in the Clinical Trials section of labeling.

Dosage and Administration

Language has been altered to describe the circumstances in which a dose of 20 mg can be given, as discussed in our 8/4/99 meeting with the sponsor.

Finally, as described by Dr. Laughren and Dr. Seevers, Chemistry Team Leader, the sponsor's approved inspection status expired in 6/99 (as a matter of course). We have just received an updated EER from Compliance; therefore, this issue has been resolved.

RECOMMENDATION

The application should be approved with the attached label.

Cc:
NDA 20-859
HFD-120
HFD-120/Katz/Laughren/Mille

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: August 11, 1999

/S/ [redacted]

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for
Sonata (zaleplon) for the Treatment of Insomnia

TO: File NDA 20-859
[**Note:** This overview should be filed with the 2-26-99 submission.]

1.0 BACKGROUND

In our 1-6-99 approvable letter, we requested a regulatory status update, a world literature update, and a phase 4 commitment [redacted] We did not ask for an additional safety update, but rather, noted that the 10-22-98 safety update was under review. We acknowledged receipt of an 11-24-98 chemistry submission that would not be reviewed in the original review cycle, but rather, asked them to incorporate it by reference as part of their response to the other deficiencies. We identified our preferred dissolution methodology and specifications. We also attached our proposal for labeling.

Wyeth-Ayerst responded to our approvable letter with a 2-26-99 submission, including an alternative labeling proposal and responses to the other questions and requests in our letter. In additon, Wyeth-Ayerst submitted a 3-18-99 rationale and draft protocol for a pediatric sleep study in support of a request for a Written Request.

The review team, up to the level of Team Leader, interacted with the sponsor over a period of several months, including both exchanges of draft labeling and teleconferences in order to resolve most of the less controversial differences in labeling prior to our face-to-face meeting with Wyeth-Ayerst on 8-4-99. At that meeting, we reached final agreement on labeling on all issues except that of a patient package insert (PPI). An 8-9-99 telcon was held to discuss the issue of a PPI (see discussion under 9.0 Labeling/PPI), and we reached agreement on slightly revised language for the PPI by exchange

of faxes on 8-10-99. The mutually agreed upon final labeling [SONATALABAP6.DOC] is included with the approval letter.

Dr. Paul Andreason reviewed the 10-22-98 safety update.

2.0 SAFETY UPDATE

The safety update included reports of serious adverse events (SAEs), adverse dropouts, and other adverse events for new patients and new information for existing patients. The safety update covered a period from 10-1-96 through 6-30-98 for the non-Japanese studies and from 6-1-97 through 6-30-98 for the Japanese studies. All of the new safety data for non-Japanese patients came from open studies. New safety data from Japanese patients came from short-term controlled trials.

-For the non-Japanese patients, the focus was on SAEs and adverse dropouts; there were no deaths. There were 2 reports of seizure. While neither case can be definitively attributed to zaleplon, they will be noted in labeling. There were 2 reports of modest transaminitis associated with zaleplon treatment that were not otherwise explained. Abnormalities in liver function tests is already noted in "Other Events." There was also a case of vertigo, however, this event already appears in the 1% table. Otherwise, the new safety findings were not noteworthy.

-There was no new pertinent safety information from the Japanese studies.

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The sponsor's literature update covered the period from Feb, 97', the cut-off date for the original literature review, and Dec, 98.' A listing of titles of 16 published papers and titles of 13 abstracts of presentations were provided in the 2-26-99 response to the approvable letter. Timothy Whitaker, MD, the medical monitor from WA, reviewed these materials and provided a warrant that there were "no findings that would adversely affect the conclusions about the safety of Sonata." I reviewed the titles of these papers and abstracts and saw nothing that was suggestive of new important safety information.

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The sponsor noted in the 2-26-99 submission that Sonata applications have been filed in 24 nonUS countries. While positive preliminary opinions have been granted in the 15 European countries, final approval has not yet been granted in any country. Thus, there were no approved foreign labels available for review.

5.0 PEDIATRIC STUDY REQUEST

We initially responded to the 3-18-99 request for a Written Request with a 6-7-99 letter indicating that we would be unable to issue a Written Request until we could determine, with the help of the pediatric advisory committee, whether or not it would be appropriate to encourage development of Sonata in pediatric populations. The final approval letter will include standard language provided by the pediatric committee regarding the deferral of pediatric studies until the above determination can be made.

6.0 CHEMISTRY DEFICIENCIES

It is my understanding that all remaining CMC issues have been resolved as of this time, with the exception of an expired EER. It is my impression that this kind of deficiency would not ordinarily be considered sufficient justification for delaying a final approval action. In any case, we will forward the approval package to the Office, noting this deficiency.

7.0 REQUEST FOR PHASE 4 [redacted]

[redacted]

8.0 DISSOLUTION SPECIFICATION

We have reached agreement with the sponsor on a dissolution method and specifications, and these details are included in the approval letter.

9.0 LABELING/PPI

A major issue in our labeling negotiations involved the question of how best to characterize dose response information for safety and effectiveness. The sponsor's preferred approach was to try to distinguish between the 20 mg dose as a dose that was too risky to justify its marginal advantages over the lower doses, which they considered effective and essentially free of any important risks. We argued against this approach, suggesting rather that there is dose dependency for both safety and efficacy, and further, that the dose may need to be individualized for certain patients in order to achieve the optimal response. Clearly, the plasma concentration actually achieved with any given

dose would in part be determined by the size and weight of the patient. Ultimately, we were able to reach agreement on labeling language to address this issue.

It came to our attention very late that WA, although it had agreed to the inclusion as the last section in labeling a section entitled "Information for Patients Taking Sonata" that is written in a way intended to be read by patients, did not intend to print this section as an independent and free-standing patient package insert (PPI). This had always been our intent, consistent with our approach for all other recently approved hypnotics, even though we had inadvertantly omitted language from the approvable letter to explicitly require an independent PPI. After some discussion with WA, we have obtained their agreement to print this section as a PPI and make it available for distribution at the time of drug dispensing. In the context of these discussions, we agreed on 2 very minor revisions of the language for this section One change involved acknowledgement that tolerance has not been observed in outpatient clinical trials with zaleplon for up to 4 weeks duration, but with a note that it is unknown whether or not the benefits of zaleplon persist beyond 4 weeks. The other change involved advice to patients to alert their physicians if they suffered from depression. The approval letter includes language noting our agreement that the PPI will be an independent document available for distribution to patients.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Wyeth-Ayerst has submitted sufficient data to support the conclusion that zaleplon is effective and acceptably safe in the treatment of insomnia. I recommend that we issue the attached approval letter with the version of labeling for which we were able to reach mutual agreement with the sponsor.

cc:
Orig NDA 20-859
HFD-120
HFD-120/TLaughren/RKatz/PAndreason/MMille
HFD-100/RTemple

DOC: MEMZLHYP.AP1

M.H. Copy

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-859

Wyeth-Ayerst Laboratories
Attention: Roy J. Baranello, Jr.
P. O. Box 8299
Philadelphia, PA 19101

JAN - 6 1999

Dear Mr. Baranello, Jr.:

Please refer to your new drug application (NDA) dated December 30, 1997, received January 6, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sonata (zaleplon) 5 mg & 10 mg capsules.

We acknowledge receipt of your submissions dated:

April 8, 1998	June 4, 1998	June 22, 1998	July 1, 1998
July 1, 1998	July 2, 1998	July 8, 1998	August 18, 1998
September 23, 1998	September 28, 1998	October 1, 1998	October 22, 1998
October 28, 1998			

We also acknowledge receipt of your submission dated November 24, 1998, that responds to our October 8, 1998 information request letter regarding chemistry section of this NDA. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies in this letter.

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

CLINICAL

1. Labeling

Accompanying this letter (ATTACHMENT) is the Agency's proposal for the labeling of Sonata. We believe it presents a fair summary of the information available on the benefits and risks of zaleplon. Please use the proposed text verbatim.

We have proposed a number of changes to the draft labeling submitted in your original December 30, 1997 submission, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. Division staff would be happy to discuss these proposed changes in detail, and we would be happy to meet with you to discuss any disagreements you might have with any part of the proposed labeling format or content.

2. Safety Update

Our assessment of the safety of zaleplon is based on our review of all safety information provided in your original submission dated December 30, 1997. We have received your safety-update amendment dated October 22, 1998, and it is under review.

3. Regulatory Status Update

Please provide any new information on the regulatory status of zaleplon worldwide. We require a review of the status of all actions with regard to this drug, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. In addition, we ask that you provide us any current foreign labeling for zaleplon, if appropriate, along with English translations when needed. It is only necessary to provide information that is more recent than that provided in your original December 30, 1997 submission.

4. World Literature Update

Prior to the approval of zaleplon, we require an updated report on the world's archival literature pertaining to the safety of zaleplon. This report should include only literature not covered in your previous submissions. We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of zaleplon. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

BIOPHARMACEUTICS

1. We ask that, as a phase 4 commitment [redacted]

dose would in part be determined by the size and weight of the patient. Ultimately, we were able to reach agreement on labeling language to address this issue.

It came to our attention very late that WA, although it had agreed to the inclusion as the last section in labeling a section entitled "Information for Patients Taking Sonata" that is written in a way intended to be read by patients, did not intend to print this section as an independent and free-standing patient package insert (PPI). This had always been our intent, consistent with our approach for all other recently approved hypnotics, even though we had inadvertantly omitted language from the approvable letter to explicitly require an independent PPI. After some discussion with WA, we have obtained their agreement to print this section as a PPI and make it available for distribution at the time of drug dispensing. In the context of these discussions, we agreed on 2 very minor revisions of the language for this section One change involved acknowledgement that tolerance has not been observed in outpatient clinical trials with zaleplon for up to 4 weeks duration, but with a note that it is unknown whether or not the benefits of zaleplon persist beyond 4 weeks. The other change involved advice to patients to alert their physicians if they suffered from depression. The approval letter includes language noting our agreement that the PPI will be an independent document available for distribution to patients.

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APPEARS THIS WAY ON ORIGINAL

cc:
Orig NDA 20-859
HFD-120
HFD-120/TLaughren/RKatz/PAndreason/MMille
HFD-100/RTemple

DOC: MEMZLHYP.AP1

COMPLETED MAR 2 2 1999

MAR 19 1999

NDA 20-859
Drug Name: Zaleplon Capsules (Sonata ®)
Indication: Insomnia
Type of submission: Labeling and Phase 4 commitment
Date of submission: 2/26/1999
Reviewer: Rae Yuan , Ph.D.

This submission contains labeling and response to the phase 4 commitments requested in [redacted]

Comments:

1. Although it is true that zaleplon produced minor effect on pharmacokinetics of all these compound, it did not exclude the possibility that zaleplon may exert some inhibitory effect on a compound having lower Km or more prominent involvement of a particular enzyme. Considering the fact that none of the listed compound, except warfarine, are prototype substrate of a particular enzyme, a study investigating the effect of zaleplon on CYP enzymes should be conducted. Such a study may be conducted in vitro using appropriate substrate and experimental conditions.

2. In the labeling, the statement under the "CLINICAL PHARMACOLOGY/Pharmacokinetics/*Race:* With the exception of the Asian population, there were no significant differences in the pharmacokinetic profile of zaleplon among different racial groups, including white, black, and Hispanic..." is misleading. In fact, the pharmacokinetics of zaleplon in ethnic groups other than Japanese and Northern Americans have not been studied. It is not certain at this point if the difference in kinetics is due to the genetic or cultural difference. Therefore, this statement should be corrected as suggested in the Jan. 6 letter from the agency.

Date of Signature: /S/ [redacted] /S/ [redacted] 3/18/99
Primary Reviewer: Rae Yuan, Ph.D
Team Leader: Chandra Sahajwalla, Ph.D /S/ [redacted] 3/18/99
Office of Clinical Pharmacology and Biopharmaceutics/ Division I
CC list: HFD-120; HFD-860 (Yuan, Sahajwalla, Mehta); CDR (Barbara Murphy)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-859

Con F. Hrsky

Wyeth-Ayerst Laboratories
Attention: Mr. Kenneth R. Bonk
P. O. Box 8299
Philadelphia, Pennsylvania 19101-8299

JUN 30 1999

Dear Mr. Bonk:

Please refer to your pending new drug application dated December 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sonata (zaleplon) capsules.

We also refer to your submissions dated November 24, 1998, February 17, 1999 and February 26, 1999, which respond to chemistry deficiencies communicated to you in an Agency letter dated October 8, 1998.

We are reviewing the above mentioned amendments to the Chemistry section of your application and have the following comments and information requests:

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

1. As noted in our October 8, 1998 letter to you, "conforms" is not acceptable when numerical results are available. We ask that you commit to providing appropriate numerical results for all release and stability testing for both drug substance and drug product where numerical values are used to define the specification.

2. We acknowledge your packaging equivalence protocol and testing results which were submitted in the 11/25/98 amendment. These data and approach may be useful as part of future proposals to amend this NDA for certain packaging changes on a post approval basis. As stated in comment 11 of our October 8, 1998 letter, stability data needs to be presented for all to-be-marketed container closure systems. Comment 11 from that letter is still applicable and it is also copied below for your convenience.

   Comment 11 from 10/08/98 Agency letter: "At this time, the seven container closure configurations listed on page 282 of Volume 1.6 are eligible for approval subject to the comments concerning them elsewhere in this letter (*vide infra*). Please note that other packaging configurations corresponding to those listed on page 2 of Volume 1 or elsewhere cannot be approved for to-be-marketed product at this time because no drug product stability data with them have been provided. If you wish additional container closure systems to be approved, that may be applied for post approval.

Alternatively, you may provide full ICH stability data for additional container closure systems (at commercial batch size) as an amendment to this NDA."

3. The following comments refer to your proposed drug product stability protocol provided on page 7 of the February 17, 1999 amendment. Your proposal for reduced stability testing after the first year of commercial marketing cannot be approved at this time. Full stability testing needs to be provided for until a significant body of stability data on marketed drug product are generated post approval and your proposal for reduced testing is submitted via an appropriate prior approval supplement. Please update your proposed stability protocol to reflect this. In your response please clarify which tests will be performed at each testing time point.

4. [redacted]

5. [redacted]

6. We remind you of your 11/25/98 commitment to provide an updated methods validation package once final agreements are reached.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of 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. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, please contact Mr. Merril Mille, Senior Regulatory Management Officer, at (301) 594-5528.

Sincerely yours,

/S/ [redacted] 6/30/97

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drugs
Products, (HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-859

Wyeth-Ayerst Laboratories
Attention: Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs
P. O. Box 8299
Philadelphia, PA 19101

JUN - 7 1999

Dear Mr. Baranello, Jr.:

Please refer to your correspondence dated March 18, 1999, requesting FDA to issue a Written Request under Section 505A of the Federal Food, Drug, and Cosmetic Act for Sonata (zaleplon).

We note that this submission provides a rationale and a draft protocol for a study of zaleplon in adolescents with delayed sleep phase syndrome. This submission also refers to page 2 of the Agency guidance document titled, "Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act" in support of a request for issuance of the Written Request prior to approval as a requirement to qualify for pediatric exclusivity.

We have reviewed your proposed pediatric study request and are unable to issue a Written Request at this time. We are in the process of assimilating information and obtaining external opinion to make a determination if a health benefit would be gained or not gained by studying children for the treatment of insomnia and, if yes, what ages in the pediatric population would be appropriate to study. Until the Agency has completed the determination, a Written Request will not be issued.

Furthermore, the qualification of this application for pediatric exclusivity will not be in jeopardy if the Agency does not issue a Written Request prior to approval. If the Agency makes a determination in the future that it would be a health benefit to study pediatric patients for the treatment of insomnia, the Written Request letter would be issued to an approved new drug application under section 505A(c) of the Act rather than 505A(a).

If you have any questions, please contact Mr. Merril Mille, Senior Regulatory Management Officer, at (301) 594-5528.

Sincerely yours,

/S/ [redacted]

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-859

APR 12 1999

Miller

Wyeth-Ayerst Laboratories
Attention: Roy J. Baranello, Jr.
P.O. Box 8299
Philadelphia, PA 19101

Mr. Baranello, Jr.:

Please refer to your new drug application dated December 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sonata® (zaleplon) Capsules, 5 mg and 10 mg and to your amendments dated November 24, 1998, February 2, 1999, and February 26, 1999.

We note that our March 8, 1999 letter acknowledged receipt of your February 26, 1999 amendment on March 1, 1999 and stated your resubmission was considered a class 1 response to our January 6, 1999 action letter. The primary user fee goal date was set at May 1, 1999.

As our review progressed, however, we realized that our initial classification of your resubmission was in error. In actuality, the November 24, 1998, February 2, 1999, and February 26, 1999 submissions together constitute a complete response to our action letter. As a result of this reassessment, we now consider your resubmission as a complete, class 2 response. Therefore, the user fee goal date has been changed to September 1, 1999.

Should you have any questions concerning this NDA, contact Merril Mille, R.Ph., Senior Regulatory Management Officer, at (301) 594-5528.

Sincerely,

/S/ [redacted] 4/9/99

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Mille

NDA 20-859

Wyeth-Ayerst Laboratories
Attention: Roy J. Baranello,Jr.
P.O. Box 8299
Philadelphia, PA 19101

MAR 8 1999

Dear Mr.Baranello, Jr.:

We acknowledge receipt on March 1, 1999 of your February 26, 1999 resubmission to your new drug application for Sonata® (zaleplon) Capsules, 5 mg and 10 mg.

The February 26, 1999 resubmission provides revised draft labeling, a worldwide regulatory status update, a world literature update, and biopharmaceutics information submitted in response to our January 6, 1999 action letter.

We consider your February 26, 1998 resubmission to be a complete, class 1 response to our January 6, 1999 action letter. Therefore, the primary user fee goal date is May 1, 1999 and the secondary user fee goal date is July 1, 1999.

If you have any questions, contact Merril Mille, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

/S/ [redacted] 3/5/99

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

[redacted]

WYETH-AYERST RESEARCH

Division of American Home Products Corporation

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FAX: (610) 964-5973

US REGULATORY AFFAIRS

August 5, 1999

Originally Sent via Telefax (Mr. Merril Mille)
Sonata® (zaleplon) Capsules
NDA No. 20-859

Russell Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn.: Document Control Room 4008
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

Reference is made to our pending new drug application, NDA No. 20-859, for Sonata® (zaleplon) Capsules submitted on December 30, 1997.

Reference is also made to the August 4 meeting between FDA and Wyeth-Ayerst regarding the proposed package insert for Sonata. As requested, revisions have been made to the package insert based upon the discussion and agreements made during the meeting. Two other minor changes have been made to the package insert. This includes a modification to the last sentence of the subsection entitled "Other Withdrawal-Emergent Phenomena" as discussed via a telephone conversation today between Mr. Mille and Mr. Bonk. Additionally, the introduction to Table 1 - Incidence (%) of Treatment-Emergent Adverse Events in Long-Term (28 Nights) Placebo-Controlled Clinical Trials of Sonata was modified to reflect the change in the table's data presentation as agreed upon during the August 4 meeting.

Attachment 1 provides the revised package insert in a clean format; Attachment 2 provides the revised package insert in a strike-out/shading format. Modifications to the package insert are found on pages 28 and 35-41 of this submission.

If there are any questions regarding this submission, please contact our representative, Mr. Kenneth R. Bonk, at (610) 902-3103.

Sincerely,

WYETH-AYERST LABORATORIES

Kenneth R. Bonk for

Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs

[redacted]

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

ORIG AMENDMENT

July 29, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

JUL 30 1999

N (BC)

DUPLICATE RECEIVED HFD-120

Originally Sent via Telefax (Dr. Rik Lostritto)
Sonata® (zaleplon) Capsules
NDA No. 20-859

Russell Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn.: Document Control Room 4008
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

Reference is made to our pending new drug application, NDA No. 20-859, for Sonata® (zaleplon) Capsules submitted on December 30, 1997.

Reference is also made to the July 23 teleconference between FDA and Wyeth-Ayerst regarding various CMC topics. More specific reference is made to the discussion regarding Wyeth-Ayerst's plan to use [redacted] bottle sizes (40 ml and 60 ml) that are bracketed by bottle sizes used in our stability studies (30 ml and 100 ml). As a result of our discussion, the Agency requested that we provide a side-by-side comparison of the container-closure components for the respective pairs (30 ml vs. 40 ml and 60 ml vs. 100 ml). This information is provided in Attachment 1. As stated during the teleconference, the composition of the components and supplier for the components are identical for the container-closure systems. The only exception is the bottle mouth and cap diameter for the 60 mL [redacted] bottle is smaller (28 mm vs. 38 mm) than the mouth and cap diameter of the 100 mL [redacted] bottle.

If there are any questions regarding this submission, please contact our representative, Mr. Kenneth R. Bonk, at (610) 902-3103.

Sincerely,

WYETH-AYERST LABORATORIES

Kenneth R. Bonk for

Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs

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WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

DUPLICATE

NC

NEW CORRESP

July 22, 1999

Sonata® (zaleplon) Capsules
NDA No. 20-859

Briefing Package for
August 4, 1999 Meeting

Russell Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn.: Document Control Room 4008
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

Reference is made to our pending new drug application, NDA No. 20-859, for Sonata® (zaleplon) Capsules submitted on December 30, 1997.

Reference is also made to the approvable letter dated January 6, 1999, our response dated February 26, 1999, and subsequent faxes containing additional FDA proposed labeling dated May 6, 1999 and July 6, 1999. Reference is also made to the scheduled August 4, 1999 labeling meeting between Wyeth-Ayerst and FDA.

Wyeth-Ayerst acknowledges the substantial time and effort that the Division of Neuropharmacological Drug Products has already put forth regarding the development of appropriate labeling for this new hypnotic, and also the perspective that was provided in each of the above versions by Dr. Thomas Laughren. Due to these efforts, Wyeth-Ayerst is in agreement with the majority of the draft labeling. Unfortunately, however, we are not in full agreement on two very important issues; these are the proposed recommendations for the Dosage and Administration section and the characterization of the rebound effects of Sonata contained in the Clinical Trials and Dependence sections of the labeling. Hence, our request for the August 4, 1999 meeting with Dr. Temple, Dr. Laughren, and yourself.

The purpose of this submission is to provide FDA with a meeting briefing package (attachment 1) that provides our current proposed labeling for these sections, as well as a summary of relevant data from our clinical trials providing the rationale for our proposed labeling. It is our intention that the August 4 meeting be used to discuss the remaining unresolved labeling issues and to reach agreement on mutually acceptable wording. Hence, we hope that all other activities regarding the review of this application will proceed such that finalizing labeling at this meeting will be the remaining step.

With regard to the dosage recommendations, we continue to believe that doses higher than 10 mg should not be recommended. As demonstrated in the clinical trial results summarized in this submission, there is a minimal increase in efficacy with 20 mg of zaleplon in comparison to 10 mg while the incidences of certain undesirable side effects increase. Accordingly, it is our preference not to recommend use of the 20 mg dose.

In addition to the changes to the dosage recommendations and characterization of rebound insomnia, three other minor changes in the FDA's July 6 labeling are also being provided. These are described below and a copy of the revised package insert incorporating all of the proposed labeling changes is provided as attachment 2. The changes are:

1. To the **Drug-Drug Interactions** subsection of the **CLINICAL PHARMACOLOGY** section, for the sake of completeness, the drugs ibuprofen, diphenhydramine, and thioridazine were added to the sentence that states [redacted].
2. The ***Mutagenesis*** subsection of the **PRECAUTIONS** section was revised to be consistent with FDA's June 14, 1999 fax regarding this subsection. We have incorporated the wording requested by FDA.
3. In the **Safe Use of Sleeping Medicines** subsection of the **INFORMATION FOR PATIENTS TAKING SONATA** section, the phrase [redacted] was removed (no. 13) from the package insert as a result of the FDA's analyses and conclusions regarding this specific subpopulation.

If there are any questions regarding this submission, please contact our representative, Mr. Kenneth R. Bonk, at (610) 902-3103.

Sincerely,

WYETH-AYERST LABORATORIES

Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs

Desk Copies: Dr. Robert Temple, Director, Office of Drug Evaluation 1
Eight additional copies are also provided (sent to Mr. Mille).

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

July 13, 1999

Sonata® (zaleplon) Capsules
NDA No. 20-859

CENTER FOR DRUG EVALUATION AND RESEARCH

JUL 15 1999

RECEIVED HFD-120

Russell Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn.: Document Control Room 4008
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

DUPLICATE NEW CORRESP

NC

Dear Dr. Katz:

Reference is made to our pending new drug application, NDA No. 20-859, for Sonata® (zaleplon) Capsules submitted on December 30, 1997.

Reference is also made to Wyeth-Ayerst's July 8, 1999 written response to the FDA's June 30, 1999 letter which provided comments and requests regarding the review of the chemistry section of the NDA. This submission provides a replacement page for page 034 of Attachment 3 of the July 8, 1999 submission regarding Specifications and Analytical Methods for the Drug

[redacted]

If there are any questions regarding this submission, please contact our representative, Mr. Kenneth R. Bonk, at (610) 902-3103.

Sincerely,

WYETH-AYERST LABORATORIES

Kenneth R. Bonk for

Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs

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WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

CENTER FOR DRUG EVALUATION AND RESEARCH

JUL 13 1999

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ORIG AMENDMENT

July 12, 1999

N (BC)

DUPLICATE

Sonata® (zaleplon) Capsules
NDA No. 20-859

Russell Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn.: Document Control Room 4008
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

Reference is made to our pending new drug application, NDA No. 20-859, for Sonata® (zaleplon) Capsules submitted on December 30, 1997.

Reference is also made to the FDA's July 7, 1999 fax from the FDA's Mr. Merril Mille, requesting samples of the Sonata 5 and 10 mg gelatin capsules in order to visually compare the coloration. Please note that updated capsule descriptions were incorporated into the November 24, 1998 (p. 30) chemistry amendment. As requested, placebo capsules (i.e., shells) are provided rather than capsules containing the drug substance. Provided (attachment 1) in two separate envelopes are samples of the Sonata 5 mg ([redacted] - 5 mg on cap and SONATA on body) and 10 mg ([redacted] - 10 mg on cap and SONATA on body) capsules.

Reference is also made to the May 4, 1999 telephone conversation between the FDA's Mr. Merril Mille and Wyeth-Ayerst's Mr. Ken Bonk in which it was indicated that a change in the label for the "Early Experience Kit" (submitted on April 9, 1999) was required. The specific change was the removal of the statement "Use carton to protect contents from light" since the capsules are adequately protected by the [redacted] bottle. Provided as attachment 2 is corrected labeling for the "Early Experience Kit" which provides for the omission of the above statement.

If there are any questions regarding this submission, please contact our representative, Mr. Kenneth R. Bonk, at (610) 902-3103.

Sincerely,

WYETH-AYERST LABORATORIES

Kenneth R. Bonk for

Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs

Desk copy: Dr. Rik Lostritto

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

July 8, 1999

Sonata® (zaleplon) Capsules
NDA No. 20-859

Russell Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn.: Document Control Room 4008
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

Reference is made to our pending new drug application, NDA No. 20-859, for Sonata® (zaleplon) Capsules submitted on December 30, 1997.

Reference is also made to the FDA's June 30, 1999 letter providing comments and requests regarding Wyeth-Ayerst's November 24, 1998, February 17, 1999, and February 26, 1999 responses to the Agency's October 8, 1998 chemistry deficiency letter. Accordingly, we are submitting the following items in response to the agency's June 30, 1999 letter.

1. Commitment to provide numerical results (and not the use of the term "conforms") for all release and stability testing for both drug substance and drug product where numerical values are used to define the specification.
2. Revised container-closure descriptions (Attachment 1) covering components used in our stability studies. Please note, as explained in our attached response, we are planning to use [redacted] bottle sizes (60 ml and 40 ml) that are bracketed by bottle sizes used in our stability studies.
3. Revised stability testing protocol (Attachment 2).
4. Revised drug product impurity specifications (Attachment 3). As discussed via telephone with Dr. R. Seevers on July 7, 1999 individual specifications have been set for [redacted] and the specification for total degradation products [redacted]
5. Confirmation that Wyeth-Ayerst is working with the DMF holder [redacted] to address deficiencies in DMF no. [redacted] It is our understanding that these deficiencies are not of a magnitude such as to preclude NDA approval.

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

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ORIG AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APR 12 1999

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DUPLICATE

April 9, 1999

Sonata® (zaleplon) Capsules
NDA No. 20-859

Russell Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn.: Document Control Room 4008
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz

Reference is made to our pending new drug application, NDA No. 20-859, for Sonata® (zaleplon) Capsules submitted on December 30, 1997.

The purpose of this submission is to provide (Attachment 1) draft sample bottle labeling and corresponding carton labeling (Attachment 2). This sample bottle and carton labeling has not been previously submitted and is intended to be used in the initial launch of Sonata. The container-closure system is identical to that submitted in the NDA. The corresponding carton is intended to hold six sample bottles containing seven 10 mg capsules per bottle.

If there are any questions regarding this submission, please contact our representative, Mr. Kenneth R. Bonk, at (610) 902-3103.

Sincerely,

WYETH-AYERST LABORATORIES

Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs

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WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

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NEW CORRESP

CENTER FOR DRUG EVALUATION AND RESEARCH

MAR 19 1999

RECEIVED HFD-120

March 18, 1999

Sonata® (zaleplon) Capsules
NDA No. 20-859
Proposed Pediatric Study Request

Russell Katz, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Attn.: Document Room 4008
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

Reference is made to our pending new drug application, NDA No. 20-859, for Sonata® (zaleplon) Capsules submitted on December 30, 1997 and the FDA's January 6, 1999 approvable letter. Reference is also made to the February 26, 1999 resubmission and the May 1, 1999 primary user fee goal date.

The purpose of this submission is to request the issuance of a "Written Request" for pediatric studies with Sonata. In support of this request, we are also submitting for FDA's consideration, Wyeth-Ayerst's rationale (Attachment 1) for conducting a Sonata pediatric study with the corresponding draft protocol synopsis (Attachment 2) that we propose as the basis for the Written Request.

The publication of CDER's "Pediatric Priority List" fulfilled one of the statutory requirements resulting from the November 21, 1997 enactment of the Food and Drug Administration Modernization Act of 1997. This legislation contained provisions for the Food and Drug Administration to grant a six-month period of market exclusivity to a pharmaceutical manufacturer for the conduct of a pediatric clinical trial. On June 29, 1998, the FDA provided further guidance on this matter through the issuance of a guidance for industry entitled, "Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug and Cosmetic Act."

The criteria for qualifying drugs for pediatric exclusivity that are not yet approved are described on p. 2 of this guidance document. The first of these criteria is that the Agency must issue a Written Request for pediatric studies before the approval of a NDA for the drug. Furthermore, the guidance strongly encourages applicants to submit proposed pediatric study requests to expedite the Agency's issuance of a Written Request (guidance, p. 6). Our plans for submitting a proposal for a pediatric study request was discussed with the FDA's Mr. Merril Mille on March 16, 1999. During this conversation, Mr. Mille advised that provided this request was submitted in a timely fashion, it would not have an effect on the primary user fee goal date of May 1, 1999. Accordingly, we are submitting a proposal, summarized below, for a pediatric study with Sonata that is intended to form the basis of a "Written Request" for pediatric information.

Study Rationale and Description

Of the extrinsic sleep disorders in children, circadian and scheduling disorders comprise one area in which our understanding has advanced over the past 10 years. The most common specific problem of adolescents in this category is delayed sleep phase syndrome (DSPS). Delayed sleep phase syndrome occurs in adolescents when their circadian system adapts to a pattern of delayed bedtimes and delayed morning awakenings particularly during the summer recess, holidays, and weekends. When school resumes, these adolescents have difficulty getting to school on time and often have academic and behavioral problems at school due to excessive daytime sleepiness. Current treatment for DSPS consists of chronotherapy [either phase advance (i.e., the process of shifting small consistent advances in bedtime) or further phase delay (i.e., using successive delays in bedtime)] combined with cognitive behavioral therapy. Chronotherapy and behavioral therapy is not successful in approximately 40% - 50% of the adolescents with DSPS.

Our proposed pediatric protocol is entitled:

Protocol No. 0897A-319-US

"An Evaluation of Zaleplon 5 and 10 Mg and Placebo on Sleep Performance and Alertness in Adolescents With Delayed Sleep Phase Syndrome"

The primary objective of this study is to evaluate the effect of zaleplon on latency to persistent sleep (LPS) using polysomnography (PSG) in adolescents with delayed sleep phase syndrome (DSPS). A secondary objective is to evaluate the effect of zaleplon on daytime sleepiness using the multiple sleep latency test (MSLT), digit symbol substitution test (DSST), and subjective assessment of daytime sedation (visual analog scale, VAS) in adolescents with DSPS.

This study is designed to evaluate the safety and efficacy of 5 and 10 mg of zaleplon compared to placebo in adolescents (ages 12 to 16) with DSPS. A sufficient number of patients will be enrolled to allow for the completion of 48 patients in this multi-center, randomized, double-blind, placebo-controlled, three-period crossover study in adolescents with DSPS. Each patient will participate in the study for approximately six weeks (spending 8 nights and days in the sleep lab)

consisting of a home screening phase, a PSG screen/baseline laboratory phase, a home phase, three sleep laboratory visits for sleep monitoring with two corresponding washout periods (which consist of home monitoring in combination with chronotherapy), and a final evaluation. The primary efficacy endpoint will be the mean LPS for zaleplon 5 and 10 mg treatments vs. placebo. The secondary efficacy endpoint will be the mean sleep latencies for the first nap of the MSLT. Other secondary measures include sleep variables derived from the PSG recordings, the DSST, the subjective assessment of sedation utilizing a visual analog scale, and the assessment of obtained pharmacokinetic information.

Therefore, this study will provide data about zaleplon's ability to decrease LPS in adolescents with DSPS, as well as safety and tolerability data in this patient population. Zaleplon should help the adolescent fall asleep during the phase advance stage of therapy and help to maintain the desired bedtime during the maintenance phase. If zaleplon safely and effectively reduces sleep latency in adolescents with DSPS in the proposed study, clinicians would have an additional tool for treating DSPS.

We believe that the completion and analysis of this study will provide useful pediatric information which could be incorporated into the "Special Populations" and "Clinical Trials" subsections of the Clinical Pharmacology section, the "Pediatric Use" subsection of the Precautions section, and the "Special Populations" subsection of the Dosage and Administration section of the Sonata package insert.

It should also be noted that Ambien (zolpidem), a hypnotic that is similar to Sonata, is listed in Docket No. 98N-0056 that provides a "List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population" (Attachment 3).

In conclusion, we request that the Division of Neuropharmacological Drug Products (DNDP) provide Wyeth-Ayerst with a "Written Request" for the conduct of the referenced Sonata pediatric study. In addition, we also request that the DNDP provide written confirmation that completion and submission of the referenced study will qualify Sonata for the six-month market exclusivity extension provided for under the FDA Modernization Act.

If there are any questions regarding this submission, please contact our representative, Mr. Kenneth R. Bonk, at (610) 902-3103.

Sincerely,

WYETH-AYERST LABORATORIES

Kenneth R. Bonk for

Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

February 26, 1999

Sonata® (zaleplon) Capsules
NDA No. 20-859
Complete Response to Approvable Letter

Russell Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn.: Document Control Room 4008
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

Reference is made to our pending new drug application, NDA No. 20-859, for Sonata® (zaleplon) Capsules submitted on December 30, 1997.

Reference is also made to the Agency's January 6, 1999 approvable letter in which Wyeth-Ayerst was notified that the above referenced NDA was approvable and Wyeth-Ayerst's January 6, 1999 letter notifying the FDA of our intent to amend the NDA.

We are providing complete responses to each of the following issues identified in the approvable letter. For your convenience these comments have been briefly restated and are followed by our response.

Labeling

The January 6, 1999 approvable letter included the FDA's proposal for the labeling of Sonata, and offered an opportunity to discuss the proposed changes.

Accordingly, this submission contains the following items with respect to the labeling:

1. Rationale explaining the basis for changes proposed by Wyeth-Ayerst (Attachment 1).
2. Revised draft labeling with shading and strikeout to denote changes from FDA's January 6, 1999 approvable version (Attachment 2).
3. Clean (unshaded) version of the revised draft labeling (Attachment 3).
4. Diskette containing Microsoft Word version of the draft labeling (Attachment 4).

Once the FDA has had an opportunity to consider the revised draft labeling contained in this submission, we propose that a meeting or teleconference be held in order to discuss and resolve any remaining differences regarding the content of the labeling. Wyeth-Ayerst is anxious to work with the Division to address these issues rapidly to allow for approval of this NDA.

Worldwide Regulatory Status Update

"Please provide any new information on the regulatory status of zaleplon worldwide. We require a review of the status of all actions with regard to this drug, either taken or pending before foreign regulatory authorities...."

An update on the status of all actions taken or pending before foreign regulatory authorities with regard to Sonata for the treatment of insomnia are reported in Attachment 5.

World Literature Update

"Prior to the approval of zaleplon, we require an updated report on the world's archival literature pertaining to the safety of zaleplon. This report should include only literature not covered in your previous submissions. We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of zaleplon...."

A report on the world's archival literature pertaining to the safety of Sonata for the treatment of insomnia is contained in Attachment 6.

Biopharmaceutics

[redacted]

Chemistry Issues

The January 6, 1999 approvable letter provided a recommendation by the Office of Clinical Pharmacology and Biopharmaceutics for a tighter dissolution specification for Sonata capsules. Additional reference is made to the FDA's October 8, 1998 chemistry information request letter in which the FDA provided comments or requested information concerning various chemistry issues. With the exception of one question (#12), the October 8, 1998 information request letter was replied to in Wyeth-Ayerst's November 24, 1998 amendment. Question #12 requested "appropriate tests and specifications for microbial content as per USP<23>." A response addressing this issue as well as the request for a revised dissolution specification were provided in Wyeth-Ayerst's recent February 17, 1999 submission. Thus, Wyeth-Ayerst has responded to all requests for chemistry information that were conveyed to us.

Therefore, the following items are provided in this submission to provide a complete response to the Division's January 6, 1999 approvable letter:

Attachment No.	Contents
1	Wyeth-Ayerst's rationale for proposed changes to label
2	Revised draft labeling indicating changes
3	Clean (unshaded) version of revised draft labeling
4	Diskette containing Microsoft Word version of draft labeling
5	Worldwide Regulatory Status
6	World Literature Update
7	Phase 4 commitment plan [redacted]

An additional seven desk copies have been included for your convenience. If there are any questions regarding this submission, please contact our representative, Mr. Kenneth R. Bonk, at (610) 902-3103.

Sincerely,

WYETH-AYERST LABORATORIES

Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

DUPLICATE

February 17, 1999

Sonata® (zaleplon) Capsules
NDA No. 20-859

Russell Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn.: Document Control Room 4008
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz

Reference is made to our pending new drug application, NDA No. 20-859, for Sonata® (zaleplon) Capsules submitted on December 30, 1997.

Additional reference is made to the FDA's January 6, 1999 approvable letter and the October 8, 1998 chemistry information request letter in which the FDA provided comments or requested information concerning various chemistry issues. The January 6, 1999 approvable letter provided a recommendation by the Office of Clinical Pharmacology and Biopharmaceutics for a tighter dissolution specification for Sonata capsules. With the exception of one question (#12), the October 8, 1998 information request letter was replied to in Wyeth-Ayerst's November 24, 1998 amendment. Question #12 requested "appropriate tests and specifications for microbial content as per USP<23>."

Attached is Wyeth-Ayerst's written response to the above requests. To facilitate your review, we have restated the FDA's questions/comments where appropriate. Also provided in this submission is a 36-month drug product stability report that proposes a 36-month expiry date for Sonata capsules. Attachments 1 and 2 provide supportive documentation. A complete response to the approvable letter will be forthcoming in the near future.

If there are any questions regarding this submission, please contact our representative, Mr. Kenneth R. Bonk, at (610) 902-3103.

Sincerely,

WYETH-AYERST LABORATORIES

Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs

Desk Copy: Dr. Richard Lostritto, DNDC I, Office of New Drug Chemistry
Dr. Rae Yuan, Division of Pharmaceutical Evaluation I

WYETH-AYERST RESEARCH

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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

DUPLICATE

[redacted]

January 6, 1999

Originally Sent Via Telefax (Mr. Merril Mille)

Sonata® (zaleplon) Capsules
NDA No. 20-859
Response to Approvable Letter - Intent to Amend

Russell Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn.: Document Control Room 4008
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

Reference is made to our pending new drug application, NDA No. 20-859, for Sonata® (zaleplon) Capsules submitted on December 30, 1997.

Reference is also made to the FDA's January 6, 1999 approvable letter in which Wyeth-Ayerst was notified that the above referenced application was approvable. In compliance with the approvable letter and in accordance with 21 CFR 314.110(a)(1), we hereby notify the Division that it is our intention to amend the application.

The issues to be resolved prior to the approval of this application include the FDA review of the safety update, world literature update, worldwide regulatory status, and outstanding chemistry issues, as well as development of labeling which is acceptable to both the FDA and Wyeth-Ayerst.

We look forward to working with the Division representatives to finalize the approval of this NDA. If there are any questions regarding this submission, please contact our representative, Mr. Kenneth R. Bonk, at (610) 902-3103.

Sincerely,

WYETH-AYERST LABORATORIES

Kenneth R. Bonk for

Roy J. Baranello, Jr.
Senior Director, U.S. Regulatory Affairs