CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020859

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

N20-859

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: **January 5, 1999**

FROM: **Director, Office of Drug Evaluation I**

SUBJECT: **Zaleplon (Sonata, Wyeth Ayerst), NDA 20-859**

TO: **Dr. Laughren**

Zaleplon plainly decreases sleep latency. Its short half provides both its benefits and liabilities. The principal liability is little ability to increase total sleep time or decrease awakenings; it seems to be less effective than zolpidem for this purpose and even at 20 mg shows no consistent effect on this measurement. The advantage of this is little effect on memory and psychomotor function beyond one hour (it is still important to go to bed after taking the drug; people who don't are the ones who have hallucinations, memory loss, etc.) and no next-day residual effects. It remains to be shown that there is no late night release but there seems clearly no next-day anxiety. It appears we're not convinced of the absence of rebound insomnia, but there do not seem to be withdrawal effects.

I've added comments and questions to the labeling. In addition, I'd note the following:

1. There is a large comparative database with Zolpidem. Zelaplon is clearly less effective at sleep maintenance yet seems clearly better at sleep induction. What would it take to get that clear in labeling or advertising?

2. The PD section is so stripped of potential claims it is almost valueless. Can't one say anything about comparisons to benzodiazepines?

3. Why don't we want to know (in vitro at least) whether Z inhibits 3A4?

4. I believe we should clearly state that Z has little effect (certainly at 10 mg) on total sleep and awakenings; i.e., it's worse than having no data. In every case zolpidem was clearly superior on this measure. That is hardly surprising; the whole point of Z is that it disappears rapidly.

5. Labeling often has interaction information located in Clin Pharm and, as appropriate, in Precautions. In the draft labeling, it's all in Precautions. More than half of it, however, is a "no effect" statement (drugs that inhibit CYP 3A4; drugs bound to plasma protein, drugs with narrow IT, drugs that alter renal excretion).

Consider dividing in the usual fashion, pulling the 3A4 inducer data, the aldehyde oxidase data, and the CNS interaction data into Precautions.

/S/ [redacted]

Robert Temple, M.D.

cc: Behrman

[redacted]

Copy

EXCLUSIVITY SUMMARY FORM

(Modified: October 14, 1998)

Exclusivity Summary FOR NDA # 20-859 SUPPL #_____

Trade Name: Sonata Generic Name: zaleplon

Applicant Name: Wyeth-Ayerst Laboratories HFD # 120

Approval Date If Known:_____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   d) Did the applicant request exclusivity?

   YES /_X_/ NO /___/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

   FIVE

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8.**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____
Investigation #2, Study # _____
Investigation #3, Study # _____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/
Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ _____
NDA # _____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/
Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:
NDA # _____ _____
NDA # _____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):
NDA # _____ _____
NDA # _____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2
IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2
YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

/S/ [redacted]
Signature
Regulatory Management Officer

12/02/98
Date

/S/ [redacted]
Signature of Office/Division Director

12/22/98
Date

APPEARS THIS WAY ON ORIGINAL

cc: Original NDA Division File HFD-93 Mary Ann Holovac
Typed: 12/02/98

N 20-859

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20859 **Trade Name:** SONATA (ZALEPLON) CAPS 5MG/10MG
Supplement Number: **Generic Name:** ZALEPLON
Supplement Type: **Dosage Form:** CAP
Regulatory Action: AE **Proposed Indication:** short-term treatment of insomnia

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
The indication has minimal relevance for pediatric populations. No need fora specific pediatric program.

No need for specific pediatric plan.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MERRIL MILLE

/S/ [redacted]
Signature

12/02/98
Date

per. Tom Laughren

APPEARS THIS WAY ON ORIGINAL

NDA No. 20-859

PATENT INFORMATION UNDER SECTION 505(b)

SONATA™ (zaleplon capsules) is covered by U.S. Patent 4,626,538 which claims the drug substance (compound) zaleplon. The expiration date of said patent is June 23, 2003, by virtue of the Uruguay Round Agreements Act (Public Law No. 103-465). An application for extension of said date under the terms of the Drug Price Competition and Patent Term Restoration Act of 1984 will be filed upon approval of the NDA. Patent Information will be updated upon issuance of a certificate of patent term extension. The parent company of applicant is the owner of this patent. In the opinion of applicant and to the best of applicant's knowledge, there is no other U.S. patent which claims the drug for which applicant has sought approval or which claims the use of the drug for which applicant has sought approval.

WYETH-AYERST LABORATORIES

By: _____
Arthur G. Seifert
Patent Attorney

10/7/97

Patent/Exclusivity Information

1)	Active ingredient(s)	Zaleplon
2)	Strength(s)	5 mg, 10 mg
3)	Trade Name	SONATA™
4)	Dosage Form (Route of Administration)	Capsules, Oral
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	20-859
7)	Approval Date	TBD
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug and Cosmetic Act, no ANDA may be submitted prior to 5 years after the date of approval of this NDA
9)	Applicable patent numbers and expiration date of each	U.S. Patent 4,626,538, Expiration Date: June 23, 2003

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

Item 15 B. Certification Required by Generic Drug Enforcement Act of 1992

The undersigned certifies that Wyeth-Ayerst did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306 (a) or (b)] of the Generic Drug Enforcement Act of 1992 in connection with NDA No. 20-859 for Sonata® (zaleplon) Capsules.

Signed Royd Baranello Jr

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

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

Item 15 A. Certification Required by New Drug and Abbreviated New Drug Applications Preapproval Inspection Requirements

The undersigned certifies that Wyeth-Ayerst has provided a field copy of the Chemistry, Manufacturing and Controls sections, application form, and application summary of NDA No. 20-859 for Sonata™ (zaleplon) Capsules to the Philadelphia District Office, the FDA home district office for Wyeth-Ayerst Laboratories, as required under 21 CFR 314.50 (d)(1)(v).

Signed _____
Joseph N. Bathish
Vice President, Worldwide Regulatory Affairs

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

December 30, 1997

Sonata™ (zaleplon) Capsules
Original NDA (No. 20-859)

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Leber:

In accordance with 21 CFR 314.50, Wyeth-Ayerst hereby submits a new drug application for Sonata™ (zaleplon) Capsules, a hypnotic for the treatment of insomnia. The recommended dose proposed in our draft labeling is 5 to 10 mg taken before bedtime, or after the patient has gone to bed and has experienced difficulty falling asleep. NDA No. 20-859 and User Fee ID No. [redacted] have been preassigned to this application.

Please note that in compliance with 21 CFR 314.50(k)(3) a true copy of the Chemistry, Manufacturing and Controls technical section, plus the application form and summary section of this NDA have been submitted to the Philadelphia District Office of the FDA, the home office for Wyeth-Ayerst Laboratories. The requested certification concerning this field copy plus the certification required under the Generic Drug Enforcement Act of 1992 are contained in Item 15 of this application. A check for the application fee has been submitted to the Mellon Bank, Pittsburgh, PA postal address designated for user fee payments.

Regulatory History

The original IND [redacted] for zaleplon (ZAL-846) was submitted [redacted]

A meeting to discuss the phase III clinical development plan for Sonata was conducted on November 17, 1995. The meeting purpose was to obtain FDA's agreement on the overall Phase 3 clinical development plan, adequacy of the clinical trial designs relative to the insomnia indication, and acceptability of the proposed statistical analyses plan. In general, the Division

agreed to: the number and types of clinical studies to support the planned NDA for the insomnia indication, the design of the controlled clinical studies, and the projected quantity of safety data (approximately 3,000 patients). It was requested by the Division that in addition to data on chronic insomniacs, data to support dosing recommendations for transient and acute insomniacs also be presented in the NDA. Accordingly, two additional insomnia studies (polysomnographic studies) have been conducted to support this aspect of the treatment of insomnia. One study is a phase advance study (209-GE); the other study (210-US) used the "first night effect" or transient model of insomnia that examined the efficacy of zaleplon in reducing the sleep latency in subjects who have never slept in a sleep laboratory. Subsequent to the Phase 3 meeting, a teleconference (December 18, 1995) with Dr. Hoberman, statistical reviewer, occurred regarding the statistical analyses plan. On September 17, 1996, a revised statistical analyses plan was submitted that encompassed the polysomnographic and sleep questionnaire studies.

A pre-NDA meeting to discuss the format and content of this NDA was conducted on May 7, 1997. FDA comments were obtained regarding specific data requirements and format with respect to various tables to be contained within the integrated summaries of efficacy and safety.

Overview of Clinical Program

Study Types and Patient Populations

The following clinical studies were conducted in support of the safety and efficacy of Sonata for the short-term treatment of insomnia. In phase 1 and clinical pharmacology studies, 867 subjects and patients were exposed to zaleplon. This included 748 healthy subjects, 97 patients (renally impaired, hepatically impaired, sleep apnea, and chronic obstructive pulmonary disease patients) and 22 hypnotic drug abusers. During phase 2 and 3 studies, conducted in North America and Europe, 2851 patients with insomnia were exposed to zaleplon for various durations of treatment.

Controlled Clinical Study Designs

In both sleep laboratory and outpatient studies, efficacy variables were derived from sleep questionnaires completed in the morning after dose administration. The patients answered questions regarding time to sleep onset, total time slept, number of awakenings, and sleep quality. In outpatient and sleep laboratory studies, the primary efficacy variable was time to sleep onset and latency to persistent sleep, respectively.

The sleep variables that were used to assess efficacy in sleep laboratory studies were derived from polysomnographic (PSG) recordings as well as post sleep questionnaires. PSG recordings were made for an 8-hour period after the patient received study medication. The variables measured by PSG recordings were latency to persistent sleep, total sleep time, and number of awakenings after sleep onset. The effects of Sonata on sleep staging were also derived from the PSG data.

NDA Contents

The contents of the NDA are as follows:

Item No.	Description	Volume No(s)
1	Index	1
2	Application Summary	1-2
3	Chemistry, Manufacturing and Controls	3-11
4b	Methods Validation	12
4c	Draft Labeling	13
5	Nonclinical Pharmacology and Toxicology	14-114
6	Human Pharmacokinetics and Bioavailability	115-209
8	Clinical	210-346
10	Statistical	347-437
11	Case Report Tabulations	438-725j
12	Case Report Forms	726-819
13	Patent and Exclusivity Information	1
15a	Certification for Transmittal of a True Copy of Item 3 to the Philadelphia District Office	1
15b	Certification Required by Generic Drug Enforcement Act of 1992	1

There are a total of 829 volumes.

CANDA

The proposal for the Sonata CANDA was submitted on March 20, 1997 in the pre-NDA meeting document, and CANDA demonstration files were submitted on July 16, 1997. Discussions regarding the proposed CANDA were conducted with Dr. Levin on April 11 and 30, 1997 and July 30, 1997. General input was also received via fax on July 23, 1997. During the July 30 conversation, Dr. Levin provided comments regarding the proposed CANDA and stated that overall it was acceptable.

Abuse Liability Potential

Abuse Liability Studies

The abuse liability of Sonata was assessed in various preclinical pharmacological and clinical studies. The preclinical pharmacology studies conducted included *in vitro* tissue binding studies, ancillary mechanistic pharmacology studies, discriminative studies in rodents, and various abuse liability studies in baboons. Regarding clinical studies, two abuse liability studies (the initial study was a dose finding study) were conducted. Other clinical studies included aspects that assessed: psychomotor and cognitive effects, the development of tolerance, withdrawal effects, and rebound insomnia potential.

Abuse Liability Assessment Document (ALAD)
An abuse liability assessment document that provides a basis for the formal scheduling of Sonata has been prepared based upon the results of the above-mentioned studies. The format and content of the ALAD is structured upon the guidance provided in your Division's November 30, 1995 letter. On February 13, 1997, an ALAD outline was submitted to the Division. In April 1997, a fax with some comments was received from the Division; these comments were subsequently discussed with Dr. Klein. Overall, the Division and Dr. Klein accepted our ALAD proposal. The ALAD has been submitted, in triplicate, to Dr. Michael Klein, at the Division of Anesthetic, Critical Care and Addiction Drug Products.

Recommended Scheduling
Based on the results of these studies, zaleplon is similar to other non-benzodiazepine and benzodiazepine hypnotics and Wyeth-Ayerst is recommending that it be a Schedule IV hypnotic at this time.

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

U.S. REGULATORY AFFAIRS

April 8, 1998

Originally sent via Telefax (Dr. Andreason)

DUPLICATE

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

AMENDMENT
N(BM1)

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn: Document Control Room 4008
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Leber:

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 a March 30, 1998 telephone conversation between the FDA's Dr. Paul Andreason and Wyeth-Ayerst's Mr. Kenneth Bonk. During the March 30 conversation, Dr. Andreason requested a translation of select pages from the case report form (CRF) of patient 11-207-2 who participated in a Japanese clinical trial (protocol no. L846/PE2/931007). Patient 11-207-2 was a 57-year-old Asian man who had committed suicide. This patient's original, untranslated, case report form was provided in Item 12 of the NDA located in volume 819 on pages 26-31. Accordingly, we are providing the following information:

1. the English translation of pp. 27, 29, and 30 of the CRF for patient 11-207-2 (Attachment 1),
2. A copy of the English translation of the corresponding blank CRF pages (Attachment 2), and
3. the original untranslated CRF pages 27, 29, and 30 provided in the NDA (Attachment 3).

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

[illegible]

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ORIGINAL

WYETH-AYERST RESEARCH

U.S. REGULATORY AFFAIRS

CENTER FOR DRUG EVALUATION AND RESEARCH

MAR 24 1998

RECEIVED HFD-120

March 19, 1998

NEW CORRESP

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

Ms. Jane Axelrad, Associate Director for Policy
Room 6027, HFD-005
Office of the Center
Woodmont Office Complex 2
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

NEW CORRESP

Dear Ms. Axelrad:

Reference is made to our Sonata (zaleplon) NDA (No. 20-859) submitted to the FDA on December 30, 1997 (Attachment 1).

The purpose of this correspondence is to appeal what we believe is an inappropriate assignment of the user fee receipt date for this NDA. The FDA's January 13, 1998 NDA acknowledgment letter informed Wyeth-Ayerst that the user fee receipt date for this application is January 6, 1998 (Attachment 2). Wyeth-Ayerst is in disagreement with this assigned date and believes that the correct user fee receipt date should be December 30, 1997.

As mentioned above, the NDA was submitted (by physical delivery) to the FDA on December 30, 1997. On December 30, the user fee check was sent via Federal Express to the FDA's Mellon Bank lockbox address in Pittsburgh, PA. The Federal Express receipt (Attachment 3) documents that the check was received on December 31. A letter (January 8) from Ms. Jane Muir at the FDA-Accounts Receivable Branch indicated receipt of the check by FDA on January 2, 1998 (Attachment 4).

In follow-up, telephone conversations were held between FDA's Ms. Joslyn Swann (Regulatory Policy Staff) and Wyeth-Ayerst's Mr. Ken Bonk on January 21 and 28. Subsequently, on January 29, Wyeth-Ayerst was sent another letter from Ms. Muir clarifying the information provided in the January 8 letter. It stated that FDA received payment information regarding Sonata's user fee check on January 6, with the check being deposited on January 2 (Attachment 5). As stated above, the earlier January 8 FDA letter had informed Wyeth-Ayerst that FDA received the user fee payment on January 2.

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LTH-1380

On February 10, Ms. Swann informed Wyeth-Ayerst (Mr. Bonk) by telephone that the user fee date assigned is based upon when the FDA receives notification from Mellon Bank; hence, January 6 was assigned (as stated in Ms. Muir's January 29 letter). Ms. Swann further advised that FDA has been following this procedure for assignment of user fee due dates for at least the past 2 years.

This user fee date assignment procedure applied to our Sonata NDA is inconsistent with Wyeth-Ayerst's experience, nor do we believe it to be appropriate. It has been our standard practice since the user fee requirements came into effect to send the user fee check to the FDA's Mellon Bank address via next-day delivery by Federal Express on the same day as the NDA submission. We have followed this practice for the last 6 years with our NDA submissions. In our recent experience, over the last two years with at least four different new drug applications and four different reviewing divisions, the date that the division received the NDA was used as the basis for assigning the user fee date. This was irrespective of the date when the FDA's lockbox address (c/o Mellon Bank) received and deposited the user fee check, and also irrespective of the date Mellon Bank notified FDA that it had received and deposited the check. Four examples (see Attachments 6-9) are provided for Wyeth-Ayerst products, i.e., Effexor XR (NDA No. 20-699), Verdia (NDA No. 20-736), Alesse Tablets (NDA No. 20-683), and Suprax (S-020, NDA No. 50-621). In all four of these cases, the responsible reviewing division specified the date of NDA receipt as the basis for the user fee date.

Even were it not for this experience, Wyeth-Ayerst would still question the appropriateness of the FDA policy as recently described to us. This policy is assigning a user fee date based principally upon the Mellon Bank's efficiency in processing and depositing the company's check and then notifying FDA's Accounts Receivable Branch that a check was received and deposited. We believe that companies with good user fee records with the agency should be entitled to have their review cycles begin when the agency receives the submission. Companies expend significant resources up until the day of submission of each new NDA, and it is unreasonable in our view to allow several days to elapse from that day before the review cycle begins simply because FDA's bank has not notified the agency of funds that have already been deposited. It is obviously impractical for companies to submit user fee funds prior to submitting an application to the agency, as something unexpected may then delay the submission. Furthermore, we attempt to facilitate timely payment by sending our check on the day of NDA submission via overnight mail directly to the agency's bank. Under the arrangement with which we have experience, where the NDA submission date is used, the agency still obtains the required user fee payment before the agency has barely begun the review cycle. It does not seem reasonable in our view for the agency to delay the start of the review cycle further, particularly when the factors that are being relied on are completely outside the control of the applicant.

Wyeth-Ayerst will certainly explore with agency officials how to avoid this misunderstanding with respect to future submissions. We also recognize that coming at year's end, the processing of our User Fee payment for this submission did likely fall victim to holiday staffing. At the same time, we respectfully request some accommodation with respect to the User Fee date for this NDA given our past experience and the fact that Wyeth-Ayerst funds were available to the agency well before the agency had been so advised by its bank. If the agency cannot agree to

our anticipated User Fee date of December 30, we would suggest that fairness supports the assignment of the date as no later than January 2, the date our check was deposited.

If there are any questions regarding this, please contact me at (610) 902-3794.

Sincerely,

WYETH-AYERST LABORATORIES

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

Desk Copy: Dr. Paul Leber, Division of Neuropharmacological Drug Products
Ms. Teresa Wheelous, Division of Neuropharmacological Drug Products

WYETH-AYERST RESEARCH

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FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

June 4, 1998

Originally sent via Telefax (Dr. Andreason)

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

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn: Document Control Room 4008
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Leber:

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 a March 13, 1998 telephone conversation between the FDA's Dr. Paul Andreason and Wyeth-Ayerst's Ms. Debora Monshizadegan. During the March 13 conversation, Dr. Andreason requested a table indicating years of drug exposure in patients from Groups G (all phase II and III studies) and D (parallel group, placebo-controlled studies) including any comparators. Accordingly, the following provides Wyeth-Ayerst's response.

The table that follows shows total patient-years of exposure to zaleplon, placebo, or comparators for patient Group D and for all patients/subjects in phase II/III studies except for those in Group A; therefore, the table is comprised of data from Groups D and F (described below). Group A (1- or 2-day placebo-controlled studies: 201, 202, 207, 208, 209, and 210) included crossover studies, in which patients/subjects received more than one treatment type, and so were not analyzed because of the complexity involved in analysis and the difficulty in interpreting the results in relation to the product's safety profile. These patients/subjects were treated for only 1 or 2 days, and because they represent about 12% of the population of Group G, they would provide a minimal contribution to the patient-years of exposure (450.7) obtained from the other phase II/III studies (Groups D and F).

Therefore, the second group in the table includes patients in Groups D (parallel group, placebo-controlled studies: 203, 204, 205, 301, 303, 306 [double-blind phase], 307, and 308 [double-blind phase]) and F (open-label studies: 302, 304, 306 [open-label phase], 308 [open-label phase], and 312). All patients in this combined group who received placebo or comparator were from Group D.

PATIENT YEARS OF EXPOSURE

Patient Group	Zaleplon	Placebo Rate	Comparator Rate
Group D		39.4	25.9
Zaleplon 2 mg	0.5		
Zaleplon 5 mg	32.1		
Zaleplon 10 mg	55.1		
Zaleplon 5 or 10 mg	87.1		
Zaleplon 20 mg	20.9		
Any zaleplon	108.5		
Groups D and F	450.7[a]	39.4[b]	25.9[b]

a: Group F was not analyzed by dose, because the dose of zaleplon was titrated over time for the patients in these open-label studies.
b: No patients in Group F received placebo or a comparator.

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

U.S. REGULATORY AFFAIRS

DUPLICATE

July 1, 1998

Originally sent via Telefax (Dr. Andreason)

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

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn.: Document Control Room 4008
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Leber:

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 a June 2, 1998 telephone conversation between the FDA's Dr. Paul Andreason and Wyeth-Ayerst's Mr. Ken Bonk. During the June 2 conversation, Dr. Andreason requested that statistical analyses regarding change from baseline for ECG parameters of PR, QRS, QT, and QT_c, from studies 101 and 102 be provided, as well as information regarding the timing for the administration of ECGs after dosing. These studies are entitled "Single Escalating Dose Tolerance and Pharmacokinetic Study of Zaleplon in Normal Volunteers" and "Escalating Multiple Dose Tolerance and Pharmacokinetic Study of Zaleplon in Normal Volunteers", respectively.

ECGs were obtained on-therapy in two clinical studies of zaleplon; PR interval, QRS duration, and QT interval were assessed in zaleplon studies 101 and 102. The times at which ECG recording were made relative to dose administration are as follows. For study 101, ECG recordings were made at 1.5 and 24 hours following single dose administration of placebo, 1, 5, 15, 30, or 60 mg zaleplon. For study 102, ECG recordings were made in the morning of days 2 and 11, approximately 12 to 13 hours following multiple dose administration of placebo, 15, or 30 mg zaleplon q24h in the evening of days 1 through 10. ECG recordings were also made on day 14 of the withdrawal phase in study 102.

Tables 1 and 2 (attached) report the individual baseline value, observed value at each sampling time, and change from baseline value at each sampling time (observed value - baseline value) for these ECG parameters for studies 101 and 102, respectively. Descriptive statistics for each dose group are also presented. For the 102 study, the day -2 observation was used as the baseline.

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QTc was calculated from the measured ECG parameters using Bazet's formula. Because the R-R interval was not measured directly, it was calculated from the corresponding ECG measured heart rate. Therefore, the heart rate (HR), with units of beats/minutes, was used to derive RR using equation 1 and QT_c was then calculated using equation 2.

$$RR = 60/HR \quad (1)$$

$$QT_c = QT / \text{sqrt}(RR) \quad (2)$$

Because heart rate is not recorded with as much accuracy as RR would be, the QT_c values are not as precise and should be interpreted with caution.

Each subject's ECG parameters were individually reviewed, as were group means and standard deviations. Due to the small sample size in each group, no formal statistical testing or comparisons were made.

Evaluation of PR, QRS, QT and QTc data from both the single- and multiple-dose studies do not reveal any findings suggestive of an effect of zaleplon on cardiac conduction. In general, on-study values are clinically unchanged from prestudy (i.e., baseline) values and zaleplon treated subjects exhibit no findings either quantitatively or qualitatively different from those who received placebo.

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

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

WYETH-AYERST RESEARCH

DUPLICATE

REGULATORY AFFAIRS

CENTER FOR DRUG EVALUATION AND RESEARCH

JUL 0 9 1998

RECEIVED HFD-120

July 8, 1998

Originally sent via Telefax (Dr. Andreason)

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

[redacted] AMENDMENT

N(3n1)

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Attn.: Document Control Room 4008
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Leber:

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 a June 1, 1998 telephone conversation between the FDA's Dr. Paul Andreason and Wyeth-Ayerst's Mr. Ken Bonk. During the June 1 conversation, Dr. Andreason requested adverse event tables for Group A (very short-term, 1 or 2 day, placebo-controlled, sleep-laboratory studies) and Group D (phase 2/3, parallel-group, placebo-controlled clinical studies) patients. These tables were to provide a listing of adverse events by body system for patients who discontinued due to adverse events. Percentage of patients who discontinued and patient numbers for each adverse event noted were also requested to be included. The attached provides responses to these queries.

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

REGULATORY AFFAIRS

DUPLICATE

August 18, 1998

Originally sent via Telefax (Dr. Yuan)

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

Paul D. Leber, M.D., 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

N(BB)

Dear Dr. Leber:

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 July 28, 30, and August 4, 1998 telephone conversations between the FDA's Dr. Rae Yuan and Wyeth-Ayerst's Mr. Ken Bonk (including Mr. Troy and Dr. Darwish on August 4) regarding pharmacokinetic/pharmacodynamic (PK/PD) modeling that was provided in the Sonata NDA (volume 1.115, pp. 79-83). Attachment 1 and appendices 1-6 provide Wyeth-Ayerst's responses. Dr. Yuan's requests were for the following:

1. A detailed description of the PK/PD methods used to analyze the Digit Symbol Substitution Test (DSST) data including graphs containing the predicted DSST scores based upon the pharmacokinetic values for each particular dose group (Attachment 1).
2. The output of the NONMEM program that was used in the PK/PD modeling analyses (Appendices 1-5) including a detailed description of the method of analysis (Attachment 1).
3. Plasma concentration data and pharmacokinetic parameters for individual subjects, as well as the summary statistics for each dose group (mean, SD, and %CV), for Japanese Phase I studies L846230992 and L846941002. These were the rising single-multiple-dose tolerance and pharmacokinetic in elderly subjects studies, respectively. This data can be located in Appendix 6, tables 1-12 and 13-18, respectively.

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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

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

November 24, 1998

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

Paul D. Leber, M.D., 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. Leber:

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 an October 8, 1998 information request letter from the FDA regarding the review of the chemistry section of the Sonata NDA and Wyeth-Ayerst's October 1, 1998 submission of updated drug product stability information. The following comments were made or information requested:

Drug Substance:

1. [redacted]
2.
3.
4.
5.

6. Stability Impurities:
   a) [redacted]
   b)
   c)
   d)

Drug Product

7. [redacted]
8.
9.
10.
11.
12.
13.

General

14. The holders of DMFs [redacted] have been sent deficiency letters.
15. Provide an updated methods validation document once specifications/test methods are finalized.

The attached documentation provides Wyeth-Ayerst's response to the information request letter. To facilitate your review, we have restated the FDA's questions/comments.

Please note that in response to your comments this submission includes:

- Updated Drug Substance Specifications (p. 2)
- Updated Drug Product Specifications (p. 30)
- Proposed Package Component Equivalency Protocol (p. 24)
- Protocol for Post-Marketing Stability Testing (p. 32)
- Updated [redacted] for Testing Drug Product for Strength, Content Uniformity and Identification (pp. 69-75)

It is our understanding that submission of this amendment will not result in any extension of the due date for issuance of an action letter on this application.

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-859

OCT 8 1998

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

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 submission dated October 1, 1998.

We are reviewing the Chemistry section(s) of your submission and have the following comments and information requests:

[redacted]

[redacted]

7. We note that some sources of your compendial excipients have not provided full USP/NF test results in the certificates of analysis provided in the NDA. For example, the required [redacted] testing for [redacted] is missing. Please provide written documentation, including additional sample certificates of analysis, which clearly indicate that all suppliers for all compendial excipients to be used in your to-be-marketed drug product will fully comply with USP/NF test procedures.

8. For the description test applied to the drug product and as described on page 99 of V1.6, please describe the pass/fail criteria for the individual attributes listed (e.g., poorly formed shells, cracks, leaks, dusting, etc.) as they are applied to drug product testing. Also, the referenced method for this test appears to be applicable to empty capsules. Please clarify to what items this test method is applied.

9. For strength testing of the drug product, the same number of capsules (e.g., 10) should be tested for both strengths with appropriate calculation or dilution adjustments.

10. The following comments apply to [redacted] testing for drug product.

a) Please update the test method and reporting procedure to include specifications for CL186993 and WAY155771.

b) Once the aforementioned designated impurities are individually specified, the specification for "other individual impurities" may be tightened (e.g., [redacted]).
c) As you modify these specifications we ask that you consider the points noted in comment 6 herein.

11. 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 has 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.

12. Please provide appropriate tests and specifications for microbial content as per USP<23>.

13. The following comments apply to drug product stability testing results. We note the 10/01/98 amendment which provides either 18 month or 24 month stability results for the [redacted] storage condition.

a) Designated impurity [redacted] increases on stability up to twice its initial value by 12 months at [redacted] in some cases. Please propose an appropriate specification for this impurity (e.g., [redacted]). Please also refer to comments 6b and 6c herein.

b) We note the single point stability results for [redacted] Please provide a specification for this designated impurity which is based on and reflective of the data (e.g., [redacted]. Your proposed purity specification for this substance should be in accord with that for drug substance and drug product at release.

c) Please tighten the dissolution specification so that it is more reflective of the data (e.g., [redacted] within [redacted]. Please note that dissolution results and specifications will also be considered in the Clinical Pharmacology and Biopharmaceutics review.

d) Your stability program is a [redacted] such that not all of the capsule batches in each container closure systems for each dose are fully evaluated on stability at all ICH storage conditions (i.e., 3, 9 and 18 months or 6, 12 and 24 months, etc). Please provide a clear explanation of the rationale, design and structure of your stability protocols as used in this NDA.

e) Please provide your proposed regulatory stability protocol for each strength and container closure system to-be-marketed and justify anything less than full testing.

f) Based on the long-term and accelerated stability data provided, a shelf life of 24 months is justified. You may apply for a longer shelf-life period at any time once the full long-term stability data at [redacted] becomes available and when items 13a through 13e above have been satisfactorily responded to.

14. The Holders of DMFs [redacted] have been sent deficiency letters. Please note that while DMF [redacted] is deficient, when used in conjunction with your proposed procedures, controls and specification as put forth in your NDA, the combination of the information in DMF [redacted] and the corresponding information in your NDA are potentially acceptable as a compilation pending an adequate response to the drug substance comments provided herein.

15. Please note that when specifications and/or test methods are finalized, an updated methods validation package will need to be submitted in a timely manner.

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

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, contact Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

/S/ [redacted]

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

[redacted] APPEARS THIS WAY ON ORIGINAL

2. Dissolution Specification

We ask that you agree to the following recommendation by the Office of Clinical Pharmacology and Biopharmaceutics for a dissolution method and specification for all tablet strengths:

Apparatus:	USP Apparatus II
Medium:	900 mL water at 37 ± 0.5°C
Speed:	[redacted] RPM
Specification:	Q = [redacted] at [redacted]

Additionally, please provide the Agency with a proposed completion date for all Phase 4 commitments which you agree to conducting.

Submit twenty copies of the printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

In addition, submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

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 such action FDA may take action to withdraw the application.

Should you have any questions, please contact:

Merril J. Mille, R.Ph.
Senior Regulatory Management Officer
Telephone: (301) 594-5528

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

Sincerely yours,

/S/ [redacted] 1/6/95

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT

[redacted] APPEARS THIS WAY ON ORIGINAL

NDA No. 20-859

PATENT INFORMATION UNDER SECTION 505(b)

SONATA™ (zaleplon capsules) is covered by U.S. Patent 4,626,538 which claims the drug substance (compound) zaleplon. The expiration date of said patent is June 23, 2003, by virtue of the Uruguay Round Agreements Act (Public Law No. 103-465). An application for extension of said date under the terms of the Drug Price Competition and Patent Term Restoration Act of 1984 will be filed upon approval of the NDA. Patent Information will be updated upon issuance of a certificate of patent term extension. The parent company of applicant is the owner of this patent. In the opinion of applicant and to the best of applicant's knowledge, there is no other U.S. patent which claims the drug for which applicant has sought approval or which claims the use of the drug for which applicant has sought approval.

WYETH-AYERST LABORATORIES

By: _____
Arthur G. Seifert
Patent Attorney

10/7/97

Patent/Exclusivity Information

1)	Active ingredient(s)	Zaleplon
2)	Strength(s)	5 mg, 10 mg
3)	Trade Name	SONATA™
4)	Dosage Form (Route of Administration)	Capsules, Oral
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	20-859
7)	Approval Date	TBD
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug and Cosmetic Act, no ANDA may be submitted prior to 5 years after the date of approval of this NDA
9)	Applicable patent numbers and expiration date of each	U.S. Patent 4,626,538, Expiration Date: June 23, 2003

10/7/97

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,

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

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

Item 15 B. Certification Required by Generic Drug Enforcement Act of 1992

The undersigned certifies that Wyeth-Ayerst did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306 (a) or (b)] of the Generic Drug Enforcement Act of 1992 in connection with NDA No. 20-859 for Sonata® (zaleplon) Capsules.

Signed Royd Baranello Jr

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

copy

MEMORANDUM

DATE: August 12, 1999

FROM: Russell Katz, M.D. [redacted] 8/13 99

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

Parlg

MEMORANDUM

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 to conduct additional biopharmaceutics studies. 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