CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-434

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-434

Pharmacia & Upjohn
Attention: Roma J. Thomas
Regulatory Affairs Manager
7000 Portage Road
Kalamazoo, Michigan 49001

Dear Ms.Thomas:

Please refer to your new drug application (NDA) dated December 26, 2001, received December 26, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XANAX® XR (alprazolam) Extended-release Tablets.

We acknowledge receipt of your submissions dated November 20 and December 23, 2002.

The November 20, 2002, submission constituted a complete response to our action letter.

This new drug application provides for the use of Xanax® XR for the treatment of panic disorder.

We also refer to the January 15, 2003, telephone conversation between Ms. Roma Thomas, Pharmacia Regulatory Affairs Manager, and Ms. Anna Marie H. Weikel, Project Manager of this Division, during which the final labeling was agreed upon.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the agreed upon enclosed labeling (text for the package insert and patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-434." Approval of this submission by FDA is not required before the labeling is used.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

Chemistry Issues

1. An 18-month expiry is granted for Xanax® XR Tablets in the proposed container/ closure system [60 mL bottles of 60 tablets for all strengths and foil/foil blisters for 0.5mg and 1 mg tablets].

2. We have not completed validation of the regulatory methods. However, we expect to continue to work with you to resolve any problems that may be identified.

Biopharmaceutics Issues

1. The following agreed upon dissolution method and specification has been approved for all strengths of Xanax® XR Extended-release Tablets:

Apparatus: USP apparatus I at 100 rpm
Medium: 500 ml of pH 6.0 buffer at 37°C
Specification: see Table below

	(b)-----	-----	-----	-----
1 hour	----------	----------	----------	----------
4 hours	---------	---------	---------	---------
8 hours	---------	---------	---------	---------
16 hours	----------	----------	----------	----------

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

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Senior Regulatory Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

/S/

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

Enclosure

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

/s/

Russell Katz
1/17/03 11:28:32 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-434

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-434

Pharmacia & Upjohn
Attention: Roma Thomas
Regulatory Affairs Manager
7000 Portage Road
Kalamazoo, Michigan 49001

Dear Ms. Thomas:

Please refer to your new drug application (NDA) dated December 26, 2001, received December 26, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XANAX® XR (alprazolam) Extended-release Tablets.

We acknowledge receipt of your amendments dated February 21; March 20 and 28; April 8, May 2, 14, 21 and 24; May 2, 14, 21 and 24; July 10, 11, 17 and 26, August 2; September 3, 13 and 24; and October 15, 2002.

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

Clinical Issues

1. Our analysis of Study 271 has revealed that the assumption of normality of the data has not been satisfied. For this reason, we have re-analyzed the data using a non-parametric Wilcoxon test. The results of this re-analysis yield statistically significant between-treatment differences on all of the primary outcomes. For this reason, we consider this a positive study that should be described in product labeling.

2. You have proposed that the recommended dose should be [redacted] However, the two trials that studied fixed doses of 4 and 6 mg/day failed to distinguish these doses from placebo. While we recognize that negative studies of active drugs/doses are not uncommon in patients with Panic Disorder, these two studies raise concerns about the doses you propose to recommend as being effective. This is particularly problematic, given that the two positive studies evaluated a flexible dose range, a design that does not easily permit the identification of a specific effective dose(s). For this reason, we ask you to further examine Studies 369 and 271 to attempt to determine specific effective doses. Specifically, please examine the distribution of doses achieved in these trials, and attempt to determine which doses appear to be responsible for the effects seen.

3. You have recommended that the daily dose may be given either in a once [redacted] regimen, despite the fact that you have studied only once a day dosing. You have justified the twice a day dosing regimen by the fact that the range of plasma levels achieved (Cmax and Cmin) during a day with the twice a day

schedule is approximately the same as the range of plasma levels achieved with Xanax XR given once a day and the Xanax IR given four times a day. However, this is not the approach we had previously described as being acceptable.

Specifically, in order for us to conclude that the twice a day regimen is effective in the absence of controlled trial data examining this regimen, we asked you to show that the plasma levels achieved with twice a day dosing with the XR fall between the levels achieved with the XR given once a day and the levels achieved with the IR given four times a day, at all time points during the day. That is, at all time points, the levels produced by the XR given twice a day should be "bracketed" by levels achieved by other dosing regimens shown to be effective (in this case, XR given once a day and IR given four times a day). This is the only outcome that can unequivocally be interpreted to mean that the XR given twice a day is effective. Unfortunately, this is not the case. For this reason, we cannot conclude that twice a day dosing will be an effective regimen. We are, of course, willing to evaluate any argument you have

4. Accompanying this letter as an attachment is our proposal for the labeling of XANAX ® XR for the treatment of panic disorder, with or without agoraphobia. Please submit revised draft labeling identical in content to the enclosed labeling (text for the package insert). Explanations for our proposed changes are provided in the bracketed comments embedded within the proposed text. You may request a teleconference to discuss these changes further if you wish.

5. Under 21 CFR 314.50(d)(vi)(b), we request that you provide a final safety update for XANAX® XR.

6. Please provide any new information on the worldwide regulatory status of XANAX® XR for the treatment of panic disorder, with or without agoraphobia, including the status of all actions either taken or pending before foreign regulatory authorities.

7. Prior to the approval of XANAX® XR, we will require an updated report on the world archival literature pertaining to the safety of this product for this indication.

Chemistry Issues

1. Please provide validation results which support the use of method) for its intended use. These results may be provided in the annual report.

2. Please provide the chemical names, formulas and structures for all related substances (i.e., process impurities, degradation products, etc) associated with the synthesis of Alprazolam USP drug substance.

3. We note that you have identified a of alprazolam (see NDA 18-276/CBE S-037, May 21, 2002). Please indicate whether the current t is adequate to monitor for the formation of the form of alprazolam.

4. Please provide a description of [redacted] for the storage of Alprazolam USP [redacted] bulk drug substance including the names and addresses of the [redacted] suppliers.

5. The [redacted] that are included in NDA 21-434 represent drug substance release testing at both the Kalamazoo and Arecibo facilities. Please provide a description of the acceptance testing to be performed by the [redacted] on the active ingredient lots that will be used to manufacture XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg.

6. Please provide a description of the acceptance testing that will be performed [redacted] on the compendial excipient lots that will be used to manufacture XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg.

7. Please provide a description of the proposed in-process controls (limits, tests and frequency of testing) for the packaging of XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg.

8. Please include in the Appearance Specification for XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg a description of any debossing characteristics that will be used in the manufacture of the drug product.

9. Please include a detailed description of the actions the analyst is to follow if system suitability is not met in [redacted]

10. Please provide instructions in [redacted] describing the [redacted] that are required for HPLC determination of Individual Impurities (identified and unidentified) in a XANAX® XR Tablet 0.5 mg, 1 mg, 2 mg, 3 mg.

11. Please determine for [redacted] the LOD/LOQ for the two major degradation products of alprazolam: [redacted]

12. Please provide results which demonstrate the robustness of [redacted] with regard to the detection and analysis of impurities in XANAX® XR Tablets. Please refer to the Guidance for Industry Q2B Validation of Analytical Procedures: Methodology (published November 1996) for instruction on how to perform such an analysis.

13. [redacted]

14. Please provide a detailed explanation of how the value for The Percent Dissolved (%D) is calculated in Test Assay [redacted] In particular, define the units for %D as well as provide an explanation for the terms SPGR (Specific gravity of suspension, g/mL) and Weight (Weight of suspension sample, in g).

15. Please provide the chemical structure of [redacted] as well as the proposed decomposition pathways for [redacted]

16. We recommend lowering the Total Impurities specification from NMT [redacted] to NMT [redacted] A lower Total Impurities specification for XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg is justified based on the degradant levels detected in supportive stability lots.

17. Please indicate, which [redacted] is supplying the [redacted] for the [redacted] and the [redacted]

18. Please provide the number of desiccant containers packaged in each [redacted] bottle container configuration for XANAX® XR Tablets.

19. DMF [redacted] was found to be inadequate to support NDA 21-434. Please be reminded that approval of this NDA will require that DMF [redacted] be found adequate. Alternatively, you may choose to withdraw [redacted]

20. The tablet count for the XANAX® XR blister package is listed as one tablet per blister in Table II.F-3 (see NDA 21-434, Vol. 1.4, page 64), while the proposed labeling for blister packages (see NDA 21-434,Vol. 1.2, pp 59-62) lists [redacted] per blister. Please explain this discrepancy, and describe the proposed secondary commercial package configuration for the blister packaging of XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg (i.e., number of tablets per blister strip and the number of blister strips per folding carton).

21. Please provide copies of your acceptance testing protocol (with acceptance specifications) and test methods for each primary packaging component used to package XANAX® XR Tablets.

22. Please provide a copy of the [redacted] that is used to [redacted] XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg. Until the appropriate validation of the supplier's test results are available, we request that you perform an ID test on each [redacted] lot that will be [redacted] XANAX® XR Tablets. A Specific ID test should be used (i.e., visual identification is not sufficient).

23. Please provide release-testing results (COA) for the XANAX® XR 3 mg Tablet. This data was missing from your amendment dated July 26, 2002.

24. Please indicate how long the photostability samples of XANAX® XR Tablets 0.5 mg and 3 mg, [redacted] and tablet placebos were [redacted]

25. Please provide the updated primary stability data for XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg when it becomes available.

26. You have indicated that drug release for XANAX® XR Tablets is sensitive to changes in [redacted] particle size. Describe how you plan to control the particle size of the [redacted] used to manufacture XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg.

27. Please change the storage statement on the [redacted] bottle label, the foil/foil blister label and the product insert for XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg to read:

> 'Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
> [see USP Controlled Room Temperature]'

Biopharmaceutics Issues

The effect of ethnicity on pharmacokinetics and the safety/efficacy should be further explored from available sources (such as literature and post-marketing experience from the countries outside of the U.S. where the XR formulation has been marketed) and relevant information should be incorporated into the label. We are aware of the following reports: a) Ethnic differences in the alprazolam PK parameters (Cmax, AUC, Cl, t1/2) have been reported in the literature (Lin KM et al, 1988); b) Ethnic differences in CYP3A4 enzyme activity have been reported in the literature and the CYP3A4 pathway is the major route of elimination for alprazolam.

Medication Error Prevention Issues

Your proposed trade name, container and carton labels have been referred to the FDA Division of Medication Errors and Technical Support (DMETS) for review, per current CDER review policy. DMETS has no objection to the use of the proprietary name Xanax XR. However, DMETS has identified the following areas of concern regarding the proposed container and carton labeling:

1. Revision of the established name to read "Alprazolam Extended-release Tablets" is recommended, And, increasing the prominence of the established name so that it is at least half as large as the proprietary name.

2. Your attempt to distinguish the proprietary name, Xanax XR from Xanax by placing the modifier 'XR' in a contrasting background is acknowledged. However, the current presentation of the modifier does not necessarily help to distinguish the two products. The current presentation of 'XR' looks similar to a logo and thus, it may not help to distinguish the product. It is therefore recommended that the format (font, color, and background contrast) of the modifier 'XR' be the same as the format of the proprietary name.

3. It is recommended that each strength of the immediate release and extended release formulations be distinguished by a different color. This differentiation may help to decrease selection errors between the two formulations and is particularly important in the 0.5 mg, 1 mg, and 2 mg strengths, since the two formulations have overlapping strengths. [In the current presentation, the strength (0.5 mg) on the carton labeling for Xanax and Xanax XR is presented in the same color (i.e., green).]

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
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 any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Regulatory Affairs Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

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

attachment

APPEARS THIS WAY
ON ORIGINAL

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Draft Labeling
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