CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-434

Chemistry Review(s)

NDA 21-434

XANAX® XR Tablets

Pharmacia & Upjohn

Lorenzo A. Rocca
HFD-120

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA: 21-434

2. REVIEW NUMBER: 2

3. REVIEW DATE: January 14, 2003

4. REVIEWER: Lorenzo A. Rocca, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	26 December 2001
General Correspondence	26 April 2002
Amendment #3	21 February 2002
Amendment #8	24 May 2002
General Correspondence	17 July 2002
Amendment #11	26 July 2002
Amendment #14	24 September 2002
Chemistry Review #1	18 October 2002
Amendment #16	20 November 2002
Amendment #17	23 December 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment #16	20 November 2002
Amendment #17	23 December 2002

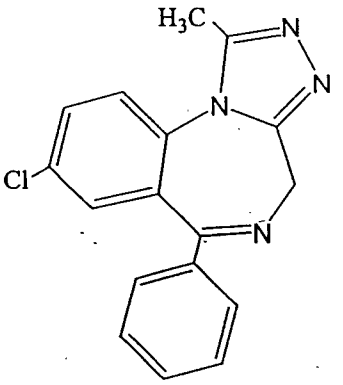
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: 8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo [4,3-*a*][1,4] benzodiazepine
Molecular Formula: $C_{17}H_{13}ClN_4$
Molecular Weight: 308.76



alprazolam

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate	May 12, 1999	N/A
	III			3	Adequate	Sept. 15, 2000	N/A
	III			3	Adequate	April 25, 2002	N/A
	III			3	Adequate	Sept. 1, 1999	N/A
	III			3	Adequate	July 28, 1999	N/A
	III			3	Adequate	Dec. 2, 1998	N/A
	III			3	Adequate	Nov. 20, 2000	N/A
	III			1	Adequate	Sept. 11, 2002	N/A
	III			3	Adequate	July 28, 2000	N/A
	III			3	Adequate	August 6, 2001	N/A
	III			3	Adequate	August 18, 2000	N/A
	III			1	Adequate	Oct. 18, 2002	N/A
	III			3	Adequate	Nov. 22, 2000	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18-276	XANAX® Tablets

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	All Sites Acceptable	8/01/02	Office of Compliance
Pharm/Tox	N/A	N/A	Aisar Atrakchi, Ph.D.
Biopharm	Overall Acceptable	10/16/02	Wen-Hwei Chou, Pharm D., Ph.D.
LNC	USAN Available	N/A	N/A
Methods Validation	Submission Pending	N/A	Lorenzo Rocca, Ph.D.
OPDRA	N/A	N/A	N/A
EA	Categorical Exclusion Granted	10/18/02	Lorenzo Rocca, Ph.D.
Microbiology	N/A	N/A	N/A

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-434

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry review perspective recommend approval of NDA 21-434. The Chemistry, Manufacturing Controls (CMC) section of NDA 21-434 is no longer deficient because the applicant has adequately responded to the CMC deficiencies in the FDA Approvable Letter dated October 25, 2002 (see NDA 21-434 Amendment No. 16 Complete Response to Approvable Letter dated November 20, 2002).

The DMF describing the was initially found to be inadequate to support NDA 21-434 and a DMF Deficiency Letter was issued (September 11, 2002). The DMF Holder has responded to the deficiencies and DMF has been re-reviewed and found adequate to support NDA 21-434 (see DMF Chemistry Review #2 dated November 18, 2002).

There are no outstanding consults or CMC related reviews pending for NDA 21-434. The Office of Compliance has found acceptable, from a cGMP standpoint, both the Alprazolam USP and the manufacturer of XANAX® XR Tablets (alprazolam) 0.5 mg, 1 mg, 2 mg and 3 mg. Please see NDA 21-434 Chemistry Review #1, dated October 18,2002, for a copy of the FDA CDER EES Detail Report.

Submission of the NDA 21-434 methods validation package, to the appropriate FDA testing laboratory, is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg are manufactured with unique shape and color for each strength (0.5 mg (pentagonal/white), 1 mg (square/yellow), 2 mg (round/blue) and 3 mg (triangular/green)). Tablets will be debossed with a "stylized X" on one side and tablet strength on the other. The sponsor plans to [redacted] The proposed secondary commercial package [redacted]

[redacted]

The drug substance Alprazolam USP [redacted] is a white to off white crystalline powder. Alprazolam is a well-known and well-defined drug substance that is the subject of official monographs in both the US and European Pharmacopoeias. In addition, the drug substance that the sponsor proposes to use to manufacture XANAX XR Tablets is identical to the drug substance already approved for the immediate release (IR) product NDA 18-278 (submitted March 2, 1979, approved October 16, 1981). It is reasonable to conclude that drug substance is well characterized. Alprazolam USP [redacted] drug substance is manufactured at the sponsor's Kalamazoo, MI facility. The sponsor has manufactured Alprazolam USP [redacted] drug substance by either [redacted] approved August 6, 1985). The sponsor has manufactured XANAX® XR Tablets using only Alprazolam USP [redacted] manufactured by the [redacted] During development of the alprazolam for IR XANAX® Tablets [redacted]) of the drug substance were identified. The sponsor has stated in their CBE supplement to IR XANAX® Tablet NDA 18-276/S-037 (submitted May 21, 2002, approved November 7, 2002) that alprazolam is [redacted] Of these [redacted] is often the major component (i.e., most thermodynamically stable) with [redacted] being easily [redacted]

Since the [redacted] it is expected that Alprazolam USP [redacted] drug substance used to manufacture XANAX®

XR Tablets will be predominately [redacted] In their NDA 18-276 supplement S-037, the sponsor has further stated that normal production [redacted] does not affect the alprazolam [redacted] In addition, the sponsor has noted in NDA 18-276/S-037 a crossover study in healthy volunteers the results of which the sponsor states shows no significant difference in bioavailability between [redacted] In light of the clinical study described in NDA 18-276/S-037, a consult was submitted to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). Biopharm found the sponsor's supplemental application S-037 submitted under NDA 18-276 acceptable, and concurred (October 30, 2002) with the sponsor that the existence of [redacted] of solid-state drug substance alprazolam is not expected to affect drug product performance. The sponsor's Alprazolam USP [redacted] to meet the following particle size tests: Less than [redacted] Alprazolam is a controlled substance under the Controlled Substance Act by the Drug Enforcement Administration, and XANAX® XR Tablets have been assigned to Schedule IV.

XANAX® XR Tablets are manufactured using excipients which are USP/NF grade, and the colorants which are certified color additives that may be safely used for coloring drugs (i.e., FD&C Blue #2 (21CFR74.1102), D&C Yellow #10 (21CFR74.1710)). The composition of the formulation is identical for the four strengths of XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg except for the amount of drug substance and absence or presence of a colorant. The sponsor has shown that the excipients are suitable from a manufacturing standpoint for the manufacture of XANAX® XR Tablets. Excipients and active [redacted] Due to drug loss during manufacturing, a [redacted] of alprazolam is required to meet label claim. The excess is reflected in the Batch Formula rather than the amount per tablet. The sponsor is committed (see NDA 21-434 Amendment #11, July 26, 2002) to recalculating the overage needed to achieve 100% label claim after they have manufactured sufficient lots (not to exceed [redacted] lots for any strength) to provide a reasonable statistical basis for the change. The sponsor has stated (and the FDA agrees) that reduction in overage for a given strength is reportable in the Annual Report following the change. The sponsor's currently marketed immediate release XANAX® Tablets are manufactured with a [redacted] overage.

[redacted] NDA 21-434 represents a new NDA for XANAX® XR Tablets. The proposed commercial formulations for NDA 21-434 are unchanged from those submitted [redacted] in the original [redacted] The clinical formulations used in the pivotal PK/PE and efficacy studies are all similar to the proposed market formulation. The differences between the clinical formulations and the market formulation are not deemed great enough from a chemistry standpoint to cause concern that comparability studies are needed.

During the development of their alprazolam XR formulation several drug release [redacted] were evaluated, and [redacted] was chosen as the [redacted]. In aqueous media, [redacted] forms [redacted] through which alprazolam [redacted] In the formulation being proposed for market [redacted] at a concentration of about [redacted] (w/w), is a [redacted]s. The [redacted] mixture of viscosity grades was found to provide the desired alprazolam plasma concentration time profiles. Alternative formulations containing [redacted] were tested *in vivo* but did not provide the desired blood level. Besides the effects of different viscosities of [redacted] on drug release the sponsor has investigated the effect of large particle size [redacted] The sponsor states that the drug release test is sensitive to changes in [redacted] particle size. [redacted] particle size has no effect on the *in vivo* absorption. The sponsor has adequately described how they plan to [redacted] used to manufacture XANAX® XR.

B. Description of How the Drug Product is Intended to be Used

The sponsor's objective was to develop an extended-release (XR) tablet that would exhibit alprazolam plasma levels within the range of the currently marketed immediate release (IR) XANAX Tablets 0.25 mg, 0.5 mg, 1 mg and 2 mg, while decreasing the variation in peaks and troughs associated with four-times-daily dosing. Each XANAX® XR Tablet contains 0.5 mg, 1 mg, 2 mg or 3 mg of alprazolam. The proposed dosing regimen is [redacted] Tablets may be administered once daily, [redacted] The tablets should be taken intact; they should not be chewed, crushed or broken.

The sponsor initially indicated that a [redacted] shelf life is important to ensure commercial viability of XANAX® XR Tablets. In subsequent discussion between Mark Amman (Senior Director, Regulatory Affairs, Pharmacia & Upjohn) and Russell Katz, M.D. (Director, Division of Neuropharmacological Drug Products (HFD-120), CDER, FDA) the sponsor has indicated that a minimum of 18-months shelf-life is needed to make this product commercially viable at the time of approval. Pharmacia & Upjohn originally submitted NDA 21-434 without any primary stability data. The sponsor's position was that based on the stability data generated [redacted] for sustained release [redacted] there was adequate stability data to permit a substantive review and support assignment of a [redacted] expiration date to XANAX® XR Tablets. In addition, the sponsor initiated a primary stability program involving 12 confirmatory XANAX® XR Tablet lots (3 lots of each strength). The confirmatory stability lots are full-scale lots that differ from the proposed market presentation only in the absence of debossing markings. The formulation, tablet shape and color and manufacturing process are the same as those proposed in NDA 21-434. The stability program will store XANAX® XR Tablets under ICH conditions in the commercial container closure system. Currently the sponsor has submitted the time zero tests results, [redacted] stability data for a subset of tablet

strengths and packages that are not intended for initial market introduction ([redacted] and [redacted]) and up to 6 months on a subset of tablet strengths and packages intended for initial market launch (i.e., XANAX® XR 0.5 mg, 1 mg, 2 mg and 3 mg in 60 mL [redacted] bottles of 60 tablets; XANAX® Tablets 0.5 mg and 1 mg in foil/foil blisters).

At the present time, all the stability data meet the specifications for XANAX® XR Tablets presented in NDA 21-434. **An evaluation of all the available supportive and primary stability data, supports a 18 month shelf life for XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg when stored at controlled room temperature 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in the proposed commercial container/closure system.**

[redacted]

[redacted]

[redacted]

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-43 is **recommended for approval** for CMC. This approval recommendation is based on the following:

- Pharmacia & Upjohn have adequately responded to all CMC deficiencies listed in the FDA's Approvable Letter dated October 25, 2002.
- DMF [redacted] was found adequate to support NDA 21-434. Approval of NDA 21-434, for CMC, requires that DMF [redacted] be found adequate to support NDA 21-434. Alternatively, the Pharmacia & Upjohn could have chosen to withdraw [redacted] from NDA 21-434. Pharmacia & Upjohn in their Complete Response to the FDA Approvable Letter dated October 25, 2002 has stated that they intend at this time to retain [redacted] of XANAX® XR Tablets.

- The applicant has provided adequate information to assure the identity, strength, quality and purity of the drug product. All facilities involved in the manufacture and control of the drug substance and drug product were found to have acceptable cGMP.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

LRocca/Date
TOliver(TL)/Date
AHomonnay(PM)/Date

C. CC Block

Orig NDA 21-434
HFD-120/Division File
HFD-120/LRocca
HFD-120/TOliver
HFD-120/AHomonnay

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Thomas Oliver
8/8/02 04:56:26 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

Redacted 90

page(s) of trade secret and/or confidential commercial information (b4)

NDA 21-434

XANAX® XR Tablets

Pharmacia & Upjohn

Lorenzo A. Rocca
HFD-120

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA: 21-434

2. REVIEW NUMBER: 1

3. REVIEW DATE: October 17, 2002

4. REVIWER: Lorenzo A. Rocca, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	26 December 2001
General Correspondence	26 April 2002
Amendment #3	21 February 2002
Amendment #8	24 May 2002
General Correspondence	17 July 2002
Amendment #11	26 July 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	26 December 2001

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Pharmacia & Upjohn
Address:	7000 Portage Road Kalamazoo, MI 49001
Representative:	Roma J. Thomas
Telephone:	616-833-4379

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: [redacted]
b) Non-Proprietary Name (USAN): alprazolam
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3 (New Formulation)
- Submission Priority: S (Standard)

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Panic disorder w/& w/out agrophobia

11. DOSAGE FORM: Extended Release Tablet

12. STRENGTH/POTENCY: 0.5 mg, 1 mg, 2 mg, 3 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ____OTC

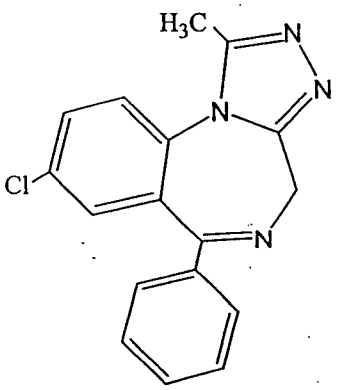
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: 8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo [4,3-*a*][1,4] benzodiazepine
Molecular Formula: $C_{17}H_{13}ClN_4$
Molecular Weight: 308.76



alprazolam

APPEARS THIS WAY
ON ORIGINAL

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate	May 12, 1999	N/A
	III			3	Adequate	Sept. 15, 2000	N/A
	III			3	Adequate	April 25, 2002	N/A
	III			3	Adequate	Sept. 1, 1999	N/A
	III			3	Adequate	July 28, 1999	N/A
	III			3	Adequate	Dec. 2, 1998	N/A
	III			3	Adequate	Nov. 20, 2000	N/A
	III			1	Adequate	Sept. 11, 2002	N/A
	III			3	Adequate	July 28, 2000	N/A
	III			3	Adequate	August 6, 2001	N/A
	III			3	Adequate	August 18, 2000	N/A
	III			1	**Inadequate**	Sept. 11, 2002	**Deficiency Letter 9/11/02**
	III			3	Adequate	Nov. 22, 2000	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18-276	XANAX® Tablets

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	All Site Acceptable	8/01/02	Office of Compliance
Pharm/Tox	Pending	N/A	Aisar Atrakchi, Ph.D.
Biopharm	Pending	N/A	Wen-Hwei Chou, Pharm D., Ph.D.
LNC	USAN Available	N/A	N/A
Methods Validation	Submission Pending	N/A	Lorenzo Rocca, Ph.D.
OPDRA	N/A	N/A	N/A
EA	Categorical Exclusion Granted	N/A	Lorenzo Rocca, Ph.D.
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-434

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing and Controls (CMC) section of NDA 21-434 is approvable from a chemistry review perspective. Before NDA 21-434 can be approved for CMC, the applicant needs to adequately respond to the following CMC deficiencies.

- Please provide validation results, which support the use of method [redacted] (particle size distribution) for its intended use. The validation results for method [redacted] may be provided in the Annual Report.
- 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 [redacted]) drug substance.
- The FDA notes that Pharmacia & Upjohn have identified a [redacted] of alprazolam (see NDA 18-276 CBE S-037, May 21, 2002). Please indicate whether the current Loss on Drying drug substance regulatory release test is adequate to monitor for the formation of the [redacted] form of alprazolam.
- Provide a description of the container/closure system for storage of Alprazolam USP [redacted]) bulk drug substance. Please include in the description of the alprazolam bulk drug substance storage system, the names and addresses of the container/closure suppliers.
- The COAs for the active ingredient lots that are included in NDA 21-434 represent drug substance release tested at both the sponsor's Kalamazoo and Arecibo facilities. Provide a description of the acceptance testing to be performed by the drug product manufacturer on the active ingredient lots that will be used to manufacture XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg.
- Provide a description of the acceptance testing that will be performed by the drug product manufacturer on the compendial excipient lots that will be used to manufacture XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg.
- 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.
- 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.
- Include in Test Assay [redacted] a detailed description of actions the analyst is to follow if system suitability is not met.
- Provide instructions in Test Assay [redacted] describing the number of [redacted] Sample Preparations 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.

- Determine for Test Assay — the LOD/LOQ for the two major degradation products of alprazolam: —
- Provide results, which demonstrate the robustness of — 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.
- For — provide the FDA with peak purity analysis results of the alprazolam peak. Please add as a system suitability requirement to Test Assay — an HPLC column efficiency of not less than — and a — for the alprazolam peak. The proposed HPLC column efficiency requirement is part of the system suitability requirements for the dissolution method in the USP for Alprazolam Tablets, which uses essentially the same chromatographic method. The — for the alprazolam peak is reported in NDA 21-434 to be Therefore, — is a reasonable system suitability requirement for —
- Provide a detailed explanation of how the value for The Percent Dissolved (%D) is calculated in Test Assay — In particular please 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).
- Provide the FDA with the chemical structure of — as well as the proposed decomposition pathways for —
- We recommend lowering the Total Impurities specification from — to NMT — 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.
- Please indicate — the cap liner for the 28mm — cap and the 45mm — cap.
- Please inform the FDA as to the number of desiccant containers packaged in each — bottle container configuration for XANAX® XR Tablets.
- DMF — product was found inadequate to support NDA 21-434. Approval of NDA 21-434, for CMC, will require that DMF — be found adequate to support NDA 21-434. Alternatively, Pharmacia & Upjohn may choose to withdraw — of the — from NDA 21-434.
- 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 — 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).

- Provide the FDA with copies of Pharmacia & Upjohn's acceptance testing protocol (with acceptance specifications) and test methods for each primary packaging component used to package XANAX® XR Tablets.
- Please provide the FDA with a copy of the COA provided [redacted] XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg. Until the appropriate validation of [redacted] esults are available, the FDA requests that Pharmacia & Upjohn perform an ID test on each package component lot that will be used to package XANAX® XR Tablets. A Specific ID test should be used (i.e., visual identification is not sufficient).
- Provide release-testing results (COA) for the XANAX® XR 3 mg Tablet. This data was missing from the sponsor's NDA 21-434 Amendment #11 dated July 26, 2002.
- Please indicate how long the photostability samples of XANAX® XR Tablets 0.5 mg and 3 mg, [redacted] and tablet placebos were [redacted]
- Please provide the FDA with updated primary stability data for XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg when it becomes available.
- The sponsor has indicated that drug release for XANAX® XR Tablets is sensitive to changes in [redacted] particle size. Describe how Pharmacia & Upjohn plans to control the particle size of the [redacted] used to manufacture XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg.
- 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]

Please note that on December 26, 2002 a Biopharm consult was submitted to the Office of Clinical Pharmacology and Biopharmaceutics (OCPD). Biopharm's review of NDA 21-434 is pending. Because the review and establishment of Dissolution Specifications and Tests is ordinarily performed by OCPD an evaluation of the sponsor's drug product stability results and in turn the drug product expiry period can not be made until final dissolution specifications are agreed to. Currently the sponsor's drug product stability results meet the drug product specifications in NDA 21-434. Because [redacted] Tablets are a non-sterile solid oral dosage no microbiological issues were reviewed for NDA 21-434.

The Office of Compliance has found acceptable, from a cGMP standpoint, [redacted] Alprazolam USP [redacted] drug substance and the manufacturer of XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg. The FDA CDER EES Detail Report is appended to this review.

Submission of the NDA 21-434 methods validation package, to the appropriate FDA testing laboratory, is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg are manufactured with unique shape and color for each strength (0.5 mg (pentagonal/white), 1 mg (square/yellow), 2 mg (round/blue) and 3 mg (triangular/green)). Tablets will be debossed with a "stylized X" on one side and tablet strength on the other. XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg will be packaged in the following package configurations: 1) 60mL (60 & Bottles with and) with , and 2) Foil/Foil ( ) blister. The sponsor needs to clarify the tablet count in their blister package (i.e., one or two tablets per blister, the number of blisters per blister strip and the number of blister strips per carton. At present, the sponsor plans Blister package labeling for XANAX® XR Tablets 0.5 mg and 1-mg strength only are provided in NDA 21-434. The sponsor will be asked to clarify whether they intend to

The drug substance Alprazolam USP is a white to off white crystalline powder. Alprazolam is a well-known and well defined drug substance that is the subject of official monographs in both the US and European Pharmacopoeias. In addition the drug substance that the sponsor proposes to use to manufacture XANAX XR Tablets is identical to the drug substance already approved for the IR product NDA (submitted March 2, 1979, approved October 16, 1981). It is reasonable to conclude that drug substance is well characterized. Alprazolam USP drug substance is manufactured at the sponsor's Kalamazoo, MI facility. The sponsor has manufactured Alprazolam USP drug substance by either their so-called ; or the later The sponsor has manufactured XANAX® XR Tablets using only Alprazolam USP manufactured by the During development of the alprazolam for immediate-release (IR)

XANAX® Tablets [redacted]) of the drug substance were identified. The sponsor has stated in their CBE supplement to IR XANAX® Tablet NDA 18-276/S-037 (submitted May 21, 2002) that alprazolam is synthesized as a [redacted]

[redacted]

In their supplement S-037, the sponsor further states that normal production [redacted] does not affect the alprazolam [redacted] form. In addition, the sponsor has recently submitted NDA 18-276/S-037 in which they describe a crossover study in healthy volunteers which the sponsor states the study results show no significant difference in bioavailability between [redacted] NDA [redacted] is current being reviewed by Biopharm for its adequacy. The sponsor's Alprazolam USP is [redacted] meet the following particle size tests: [redacted] Alprazolam is a controlled substance under the Controlled Substance Act by the Drug Enforcement Administration, and XANAX® XR Tablets have been assigned to Schedule IV.

XANAX® XR Tablets are manufactured using excipients which are USP/NF grade, and the colorants which are certified color additives that may be safely used for coloring drugs (i.e., FD&C Blue #2 (21CFR74.1102), D&C Yellow #10 (21CFR74.1710)). The composition of the formulation is identical for the four strengths of XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg except for the amount of drug substance and absence or presence of a colorant. The sponsor has shown that the excipients are suitable from a manufacturing standpoint for the manufacture of XANAX® XR Tablets. Excipients and active [redacted]. Due to drug loss during manufacturing, a [redacted] of alprazolam is required to meet label claim. The excess is reflected in the [redacted] The sponsor is committed (see NDA 21-434 Amendment #11, July 26, 2002) to recalculating the overage needed to achieve 100% label claim after they have manufactured sufficient lots (not to exceed [redacted] lots for any strength) to provide a reasonable statistical basis for the change. The sponsor has stated (and the FDA agrees) that reduction in overage for a given strength is reportable in the Annual Report following the change. The sponsor's currently marketed immediate release XANAX® Tablets are manufactured with a [redacted] overage.

[redacted] NDA 21-434 represents a new NDA for XANAX® XR Tablets. The proposed commercial formulations for NDA 21-434 are unchanged from those submitted in 1991 in the original [redacted] The clinical formulations used in the pivotal PK/PE and efficacy studies are all similar to the proposed market formulation. The differences between the clinical formulations and the

market formulation are not deemed great enough from a chemistry standpoint to cause concern that comparability studies are needed.

During the development of their alprazolam XR formulation several drug release systems were evaluated, and was chosen as the In aqueous media, forms a through which alprazolam In the formulation being proposed for market, The mixture was found to provide the desired alprazolam plasma concentration time profiles. Alternative formulations containing were tested *in vivo* but did not provide the desired blood level. Besides the effects of different viscosity's of on drug release the sponsor has investigated the effect of large particle size The sponsor states that the drug release test is sensitive to changes in particle size. particle size has no effect on the *in vivo* absorption. The sponsor will be asked to describe how they plan to control and monitor the particle size of the used to manufacture XANAX® XR.

B. Description of How the Drug Product is Intended to be Used

The sponsor's objective was to develop an extended-release tablet that would exhibit alprazolam plasma levels within the range of the currently marketed immediate release XANAX Tablets 0.25 mg, 0.5 mg, 1 mg and 2 mg, while decreasing the variation in peaks and troughs associated with four-times-daily dosing. Each XANAX® XR Tablet contains 0.5 mg, 1 mg, 2 mg or 3 mg of alprazolam. The proposed dosing regimen is Tablets may be administered once daily, evening. The tablets should be taken intact; they should not be chewed, crushed or broken.

The sponsor has indicated that a shelf life is important to ensure commercial viability of XANAX® XR Tablets. Pharmacia & Upjohn originally submitted NDA 21-434 without any primary stability data.

life for XANAX® XR Tablets 0.5 mg, 1 mg, 2 mg and 3 mg when stored at controlled room temperature 20° to 25°C (68° to 77°F) [see USP] in the proposed commercial container/closure system.

C. **Basis for Approvability or Not-Approval Recommendation**
NDA 21-434 is **approvable** for CMC. The not approval recommendation is based on the following major chemistry issues:

- Pharmacia & Upjohn needs to adequately respond to several CMC deficiencies, which are described under **Chemistry Assessment** Section VIII titled **DRAFT DEFICIENCY LETTER.**
- DMF — — — was found inadequate to support NDA 21-434. Approval of NDA 21-434, for CMC, will require that DMF — be found adequate to support NDA 21-434. Alternatively, the Pharmacia & Upjohn may choose to withdraw — — from NDA 21-434.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

LRocca/Date: Same date as draft review
TOliver(TL)/Date
AHommoney(PM)/Date

C. CC Block

Orig NDA 21-434
HFD-120/Division File
HFD-120/LRocca
HFD-120/TOliver
HFD-120/AHommoney

Redacted 90

page(s) of trade secret and/or confidential commercial information (b4)

NDA 21-434
XANAX® XR
(alprazolam) Extended-release Tablets

TABLE OF CONTENTS

(D)

Number of Pages Redacted 44

❖❖❖

Draft Labeling
(not releasable,

(D)