CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-724

CHEMISTRY REVIEW(S)

NDA 21-724

Lyrica (pregabalin) Capsules

Pfizer Global Research & Development

Thomas A. Broadbent, Ph.D.
Division of Neuropharmacological Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-724

2. REVIEW #: 1

3. REVIEW DATE: 05-AUG-2004

4. REVIEWER: Thomas A. Broadbent, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission NDA 21-446	30-OCT-2003
N-000 BC	17-FEB-2004
N-000 BC	20-APR-2004
N-000 BC	21-APR-2004
N-000 BC	22-APR-2004
N-000 BC	13-MAY-2004
N-000 BC	18-MAY-2004
N-000 BC	25-MAY-2004
NDA 21-446, CMC Review # 1	26-MAY-2004
NDA 21-446, CMC Review # 2	03-JUN-2004
NDA 21-446, TL-CMC Memorandum	04-JUN-2004
NDA 21-446, Division Director Review	29-JUL-2004
Telecon Memo	03-AUG-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Submission	30-OCT-2003
N-000 BL	17-MAR-2004
N-000 BC	28-MAY-2004
N-000 BL	01-JUL-2004
N-000 BL	02-JUL-2004
N-000 BL	09-JUL-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Global Research and Development
Address:	2800 Plymouth Road Ann Arbor, MI 48105
Representative:	Jonathan Parker, R.Ph., M.S.
Telephone:	(734) 622-5377

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lyrica
b) Non-Proprietary Name (USAN): pregabalin
c) Code Name/#: CI-1008, PD 0144723
d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 USC Sec. 505 (b) (1)

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 25, 50, 75, 100, 150, 200, 225 & 300 mg

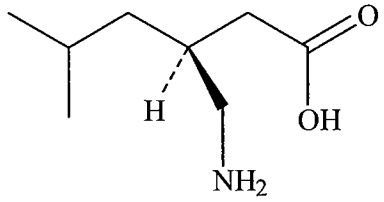
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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



(*S*)-3-(aminomethyl)-5-methylhexanoic acid
$C_8H_{17}NO_2$ Formula Weight 159.23

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

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2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
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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
IND	[redacted]	Anticonvulsant Indication, CMC information
IND	[redacted]	[redacted]
IND	[redacted]	[redacted]
NDA	21-446	Neuropathic Pain of Diabetes, CMC provisions
NDA	21-723	Neuropathic Pain [redacted]
NDA	[redacted]	[redacted]

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	2-year retest schedule for drug substance	10-MAY-2004	Karl Lin
Biometrics	24 months expiration for 25, 50, 75 & 100 mg strengths; NMT 12 month extrapolation of stability data; annual stability testing insufficient	10-MAY-2004	Roswitha Kelly
EES	Acceptable	22-JUN-2004	S. Adams
Pharm/Tox	[redacted] degradation product adequately qualified	07-APR-2004	Jerry Cott
Biopharmaceutics	Approvable Approval, with labeling recommendations	22-MAR-2004 02-JUL-2004	Sue-Chih Lee Veneeta Tandon
Methods Validation	No consult requested	--	--
ODS/DSRCS	Labeling Recommendations	03-JUN-2004	Jeanine Best
ODS/DMETS	Labeling revisions recommended & Proprietary name "Lyrica" acceptable Proprietary name "Lyrica" acceptable in reference to request from the Division of Neuropharmacological Drug Products	03-FEB-2004 20-MAY-2004	Kimberly Culley Alina Mahmud
EA	FONSI	25-FEB-2004	Florian Zielinski
Microbiology	N/A	--	--
Controlled Substance Staff	Abuse liability is found Schedule IV is recommended	31-MAR-2004	Katherine Bonson

Executive Summary Section

The Chemistry Review for NDA

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is recommended for the CMC perspective, pending resolution of labeling review.

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

In negotiations for NDA 21-446, the sponsor has committed to test the first three lots of pregabalin, manufactured at the Ringaskiddy site, [redacted] is discovered, the firm has committed to add a limit of [redacted] for this impurity to the drug substance specifications. See DACADP (HFD-170) CMC team leader's memo (6/04/04) and telecon memo (6/01/04).

II. Summary of Chemistry Assessments

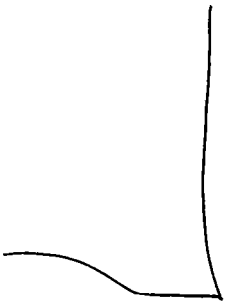
A. Description of the Drug Product and Drug Substance

Drug Substance:

Pregabalin, the drug substance for NDA 21-724, is provided by NDA 21-446. The CMC provisions have been reviewed by the CMC review team of the Division of Anesthetic, Critical Care and Addiction Drug Products (DACADP, HFD-170). Two CMC reviews have been posted.

Pregabalin is the established name (USAN & INN) of (*S*)-3-aminomethyl)-5-hexanoic acid. The molecular formula is $C_8H_{17}NO_2$. The CAS registry number is 148-50-8. The substance appears as a white to off-white crystalline solid. No characterization of odor has been given; odor is not expected,

[redacted]



Drug Product:

NDA 21-724 (epilepsy) provides for Lyrica Capsules in strengths of 25, 50, 75, 100, 150, 200, 225, and 300 mg. The lead NDA, 21-446 (diabetic neuropathic pain), provides only the strengths 25, 50, 75 and 100 mg. Lyrica Capsules are formulated with two different blends for the fill material. Blend A is —% pregabalin, —% lactose monohydrate, —% corn starch and —% talc. Blend C is —% pregabalin, —% lactose monohydrate, — % corn starch and — % talc. Blend A is used for the 25 and 50 mg strengths. Blend C is used for all other strengths. No overage is used in manufacture of the capsules. All excipients are compliant with USP/NF monographs. The capsule shells are provided by —— and comply with ONDC guidance concerning gelatin and BSE. The capsule shells are provided in sizes —— and various binary color combinations of white and/or two shades of orange. The 50 mg strength is all white with a black band. Product specifications submitted in the amendment of 18-MAY-2004 were found acceptable. —— is a degradation product as well as a DS impurity. The limit of the —— in the drug product is ——. Identification method B (HPLC) was modified so that it could distinguish pregabalin from gabapentin, a related API of similar structure. The product will be manufactured at the Pfizer facility of Vega Baja, Puerto Rico. The Office of Compliance has evaluated this facility as acceptable.

The product will be packaged in —— bottles with a capsule count of 60. Packaging in —— bottles of 30 capsules are provided for professional samples. The application also provides for professional samples in 6-capsule blister cards. Unit-dose blister packaging (a blister card of a single capsule) in packages of 100 is to be provided for hospital use.

The sponsor has proposed 36 month expiration dating for all strengths and presentations. NDA 21-446 review recommended 3-year expiration dating for the 25, 50, 75 & 100 mg strengths and 2-year expiration dating for the other strengths. This reviewer finds 36 month expiration acceptable for all strengths. The DNDCII director deems data adequate to support 36 month expiration for all presentations.

The Controlled Substance Staff has found that Lyrica has a potential for abuse and has recommended that it be classified under Schedule IV as a controlled substance.

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

Lyrica is indicated as adjunctive therapy in adults with partial seizures [redacted]. Pregabalin treatment starts with a dose of 150 mg per day and may be increased to 300 mg per day after 1 week, depending on response and tolerability. The maximum dose is 600 mg per day, which can be achieved after an additional week. Lyrica has also been proposed for other indications as provided in other applications, i.e. diabetic neuropathic pain (NDA 21-446), neuropathic pain [redacted] (NDA 21-723) [redacted]

C. Basis for Approvability or Not-Approval Recommendation

Approval for the CMC perspective is based upon the approval recommendation of the CMC review team of the Division of Anesthetics, Critical Care and Addiction Drug Products for NDA 21-446. CMC provisions of NDA 21-724 are referenced to NDA 21-446.

III. Administrative

A. Reviewer's Signature

Electronic signature in DFS

B. Endorsement Block

Chemist Name/Date: Thomas A. Broadbent
Chemistry Team Leader: Maryla Guzewska
Project Manager: Jackie Ware

C. CC Block

Chemist Name / Date: Thomas A. Broadbent
Chemistry Team Leader: Maryla Guzewska
Project Manager: Jackie Ware

22 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 2

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/s/

Thomas Broadbent
8/5/04 12:56:58 PM
CHEMIST

Maryla Guzewska
8/5/04 01:14:47 PM
CHEMIST

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA#	21-724
DATE:	03 August 2004
PRODUCT NAME:	Lyrica Capsules
SPONSOR:	Pfizer / Parke Davis
SUBJECT:	Packaging and Labeling
CONVERSATION WITH:	Jonathan Parker
TELEPHONE #	(734) 622-5377

I called Jonathan Parker 7/16/2004 to clarify provisions for packaging and labeling and left a voice-mail message. He returned my call 7/21/2004. I asked whether the NDA was to provide for blister packaging as no labeling for blisters was included in the 9-JUL-2004 labeling submission. He confirmed that blister packaging was to be provided in cards of 6 capsules (professional sample) and single-dose units in packages of 100 (hospital supplies). He called later in the afternoon to confirm that the labeling for the blisters would be the same as provided in the original 30-OCT-2003 submission for NDA 21-446.

Thomas A. Broadbent, Ph.D.
Review Chemist
Neuropharmacological Drug Products

cc: HFD-120/DivFile
HFD-120/MGuzewska
HFD-120/TBroadbent
HFD-120/JWare

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

/s/

Thomas Broadbent
8/5/04 12:16:27 PM
CHEMIST

Maryla Guzewska
8/5/04 12:41:11 PM
CHEMIST

CMC Team Leader Memo to File
NDA 21446 Lyrica (Pregabalin) capsules
Ravi S. Harapanhalli, Ph.D.
CMC Team Leader, HFD-170
Division of Anesthetics, Critical Care, and Addiction Drug Products
June 04, 2004

Overall CMC recommendation:

The NDA is recommended for approval pending an acceptable cGMP recommendation from the Office of Compliance.

CMC Reviews:

Sharon Kelly reviewed this NDA from CMC perspective. In the course of the extended review cycle of nine months (initially 6 months cycle that was extended by three months to July 28, 2004), two reviews were written based on the original NDA and the subsequent amendments resulting from information request (IR) letters sent to the firm. Her reviews were signed off into the Division Filing System (DFS) on May 24, 2004 and June 03, 2004 respectively.

Secondary review:

While critical issues pertaining to the approvability of the NDA were resolved, the following issues were discussed with Pfizer on June 4, 2004 in a teleconference and agreement was reached on all the issues except the one on two year expiration dating for the 150, 200, 225, and 300-mg strengths. Pfizer stated that they would like to discuss this issue further.

List of CMC reminders and comments resolved in the teleconference dated June 04, 2004:

1. We remind you of your commitment in the Amendment dated 13-MAY-2004 to test the first three Ringaskiddy lots of pregabalin for [redacted] If the observed levels are more than [redacted], submit the data in a prior-approval supplement and propose a specification of NMT [redacted] for this impurity.

Pfizer agreed for the proposed filing mechanism.

2. The batch reference for the [redacted] was omitted for the manufacturing example in the NDA submission, Section 3.2.S.2.2.2 page 34. Adequately document the batch reference for the regulatory starting material in all future manufacturing campaigns.

Pfizer agreed to revise their batch records to include batch reference to the regulatory starting material.

3. The data in support of a three years retest interval for the drug substance were based on only three batches from Holland; MI. Statistical analysis revealed that at end of proposed retest interval, the tolerance limits were outside the acceptable range of [redacted]. Therefore, a retest interval of two years is granted at this time. Accrual of additional stability data may qualify for a future extension of the retest interval.

Pfizer agreed to accept a retest interval of two-years for the drug substance with the understanding that this may be extended based on the accrual of satisfactory real time data.

4. Provide a revision to the drug substance specifications with the acceptance criteria for the bulk density of NLT [redacted], which is reflective of the batch experience by the proposed [redacted] This may be submitted in the next annual report.

Pfizer agreed to establish a limit of NLT [redacted] for the bulk density of the drug substance and to report it in the next annual report

5. A three year shelf life is granted only for the currently proposed configuration of the drug product, i.e. [redacted] bottles containing 60 capsules for the strengths 25-, 50-, 75-, and 100 mg.

Pfizer agreed with this recommended shelf life

6. For the strengths 150-, 200-, 225-, and 300 mg capsules, a shelf life of two years is grantable at this time. Based on the accrual of additional real time stability data on the appropriate container/closer configurations, the shelf life may be extended in the next annual report.

Pfizer stated that they would like to discuss this issue further and that they would like to present their calculations to support a shelf life of three years for these strengths.

7. Revise the post-approval stability protocol to include semi-annual testing in the first and second year of testing.

Pfizer agreed to revise their post-approval stability protocol to include semi-annual testing in the first and second year of testing.

8. Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, your continued cooperation is expected to resolve any problems that may be identified.

Pfizer agreed to cooperate with the Agency on the issue of method validation activities.

This reviewer concurs with the views of the reviewing chemist that there is no need for the validation of the analytical methods in the FDA laboratories as the analytical methods are conventional in nature and are clearly described and are adequately validated by the firm. Also they do not qualify for any of the criteria described in the interim ONDC policy on method validations.

Outstanding approvability issue:
Satisfactory cGMP recommendation from the Office of Compliance for this NDA is awaited.

Final recommendation from CMC perspective: The NDA is recommended for approval pending an acceptable cGMP recommendation from the Office of Compliance. The pending sites needing OC recommendation are the Pfizer Ireland sites. The sites have been inspected and the final report is pending for these sites.

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

/s/

Ravi Harapanhalli
6/4/04 04:13:41 PM
CHEMIST

NDA 21-446

Lyrica (Pregabalin Capsules)

Pfizer Global Research & Development

CMC Review # 2
Sharon L. Kelly
Anesthetic, Critical Care and Addiction
HFD 170

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-446

2. REVIEW #: 2

3. REVIEW DATE: June 3, 2004

4. REVIEWER: Sharon Kelly

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	30-OCT-2003
Amendment	17-FEB-2004
Amendment	21-APR-2004
Amendment	13-MAY-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s)	Document Date
Amendment	18-May-2004
Amendment	25-May-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Global Research and Development
Address:	2800 Plymouth Road Ann Arbor, Michigan 48105
Representative:	Jonathon M. Parker, R.Ph., M.S.
Telephone:	734 - 622 - 5377

8. DRUG PRODUCT NAME/CODE/TYPE: LYRICA (pregabalin) Capsules

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

- Chem. Type: 1 New Molecular Entity
- Submission Priority: P Priority Review

9. LEGAL BASIS FOR SUBMISSION: 21 USC Sec. 505 (b)(1)

10. PHARMACOL. CATEGORY: Diabetic Neuropathy Agents

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 25, 50, 75, 100, 150, 200, 225, 300 mg

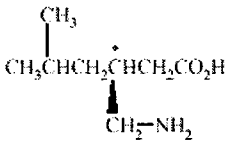
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _XX_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___X___Not a SPOTS product

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

(S)-3-(aminomethyl)-5-methylhexanoic acid $C_8H_{17}NO_2$ Mol.Wt. 159.23



* Chiral Center

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

		4	N/A		

[1] Action codes for DMF Table:
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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
IND		CI-1008 Capsules Anti Convulsant
IND		
IND		
NDA	21-723	Pregabalin Capsules Neuropathic pain
NDA	21-724	Pregabalin Capsules Epilepsy
NDA		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	2-year retest schedule for drug substance	10-MAY-2004	Karl K. Lin, Ph.D.
Biometrics	Extrapolation of no more than 12 months beyond amount of actual stability data for drug product: Two year shelf life. Yearly interval stability testing of annual batches insufficient.	10-MAY-2004	Roswitha Kelly, MS

EES	Pending, June 02, 2004		
Pharm/Tox	[redacted] degradation product adequately qualified	07-APR-2004	Jerry Cott, Ph.D.
Biopharm	preNDA Meeting: Human Pharmacokinetics and Bio - availability - Dissolution Profile	07-JUN-2000	Meeting Minutes Finalized 23-JAN-2001
Methods Validation	Pending Approval		
ODS / DMETS	Labeling revisions. Proprietary name Lyrica™ acceptable	03-FEB-2004	Kimberly Culley, RPh
EA	FONSI Recommended	25-FEB-2004	Florian Zielinski, Ph.D.
Microbiology	N/A		

The Chemistry Review for NDA 21-446

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA application can be Approved from a chemistry review perspective, pending an Acceptable EES report. The two Comparability Protocols included in this application are acceptable based upon the recommended revisions and the commitments agreed to by the Sponsor.

A [redacted] re-test period is grantable for the drug substance when stored at the recommended conditions. Data from additional batches is needed to support the Sponsor's proposal of a [redacted] re-test period.

A three year shelf life is grantable for the drug product when stored at the recommended conditions only for the currently proposed configuration ie [redacted] bottles containing 60 capsules for the 25 mg, 50 mg, 75 mg, and 100 mg capsule strengths ([redacted]). For other product configurations and strengths, the expiration period of [redacted] may be granted, which may be extended based on the on-going stability studies.

The EES report 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)

It is proposed that pregabalin capsules should be indicated for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) [redacted] as adjunctive therapy, for the treatment of [redacted] adult patients with partial seizures. The indication for this NDA and for the purposes of this chemistry review is neuropathic pain associated with DPN.

Pregabalin was developed as opaque hard gelatin shell capsules in dosage strengths of 25, 50, 75, 100, 150, 200, 225, and 300 mg. The marketed dosage strengths will be 25, 50, 75 mg and 100 mg capsules. To avoid any possible patient or pharmacist confusion, the capsules are colored, and imprinted with black ink to indicate the strength and product code, as follows:

Strength (mg)	Capsule Size	Capsule Color (Body/Cap)
25	4	White/white
50	3	White (with black ink band)/white
75	4	White/orange
100	3	Orange/orange
150	2	White/white
200	1	Light orange/light orange
225	1	White/light orange
300	0	White/orange

The issue of medical error pertaining to capsule size and color was discussed in the Agency's review divisions and the consensus is that the above combinations are acceptable.

The drug product is packaged into either ; bottles or blisters. The marketed configuration will be the bottle. However, during development, bottle configurations were in the range The configurations include seals and both child-resistant and nonchild-resistant closures, and identical liner material. The blister system is made of a blister with a foil backing.

There is no processing or sterilization needed for pregabalin manufacture. The excipient, lactose monohydrate, and the bovine gelatin used in capsule shells, are in full compliance with the Guidance "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-regulated Products for Human Use".

The Sponsor proposes a retest period for pregabalin drug substance when packaged in when stored at room temperature, or The drug substance , although not light sensitive, will be protected from light during storage according to the usual precautions. The stability data is evaluated in the Chemistry Assessment, drug substance section of this review. Statistical analysis of the data supports only a 2-year retest period for the drug substance.

The physicochemical and biological properties have been adequately characterized and are shown not to influence batch reproducibility, product performance and/or drug product quality. The impurity levels are sufficiently characterized and controlled by characteristics of the drug substance. The drug substance synthesis employs procedures that are adequately documented.

Pregabalin is crystalline It is not solvated. It is , and soluble in water. At room temperature the saturation solubility of Pregabalin in aqueous media is mg/ml in the pH range . The compound is

classified as highly soluble and highly permeable under the Biopharmaceutical Classification System (BCS). Data demonstrates that the drug product is almost completely dissolved within ——, and is independent of API particle size. The manufacture and performance of the drug product has been demonstrated over a wide range of drug substance particle size, due, in part, to the evolution of process and —— parameters at three manufacturing sites.
The drug substance IUPAC designation is (S)-3-(aminomethyl)-5-methylhexanoic acid. The synthetic route for pregabalin employs classical resolution ——, of the racemic amino acid to produce the desired (S)-enantiomer. If there is inadequate removal of the (R)-enantiomer, the amount can be reduced by applying the

The synthetic scheme employs ' —a Class II solvent according to ICH Q3C. For anticipated doses of —of pregabalin, the —is controlled at a sufficient level —— (ICH Q3C recommends —). The scheme also employs isopropyl alcohol, which is not listed in ICH Q3C, but controls are established at —— This solvent most closely resembles Class III solvents, and according to ICH Q3C, they should be limited by GMP or other quality-based requirements. Available data indicate amounts of —per day or less

The drug product manufacturing process attributes (critical parameters) have been adequately examined and have been shown not to influence batch reproducibility, product performance and/or quality. The manufacturing process consists of —— The excipients are lactose monohydrate, corn starch, and talc.

Pregabalin capsule composition has remained unchanged throughout development and commercial introduction. Changes in capsule shell color and size were made to accommodate blinding and market image aesthetics. Three different powder blends, designated as A, B, and C have been used in clinical studies. The bioequivalence of clinical formulations was demonstrated *in vitro* and a biowaiver was granted as documented in the preNDA meeting minutes of 07-JUN-2000.

The proposed commercial capsule products are filled with 1 of 2 powder blend formulations. The Series A powder blend contains —Pregabalin by weight and is used to produce 25- and 50-mg capsule strengths; Series C powder blend contains ' —Pregabalin by weight and is used to produce 75-, 100-, 150-, 200-, 225-, and 300-mg capsule strengths. Note the 150- and higher capsule strengths are not being proposed for marketing at this time for NDA 21-446.

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

Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). It interacts with an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin. Binding to the α_2-δ site is

required for analgesic, anticonvulsant and anxiolytic activity in animal models. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.

The Agency agrees to 25, 50, 75 or 100 mg capsule strengths to be given in three divided doses, to a maximum recommended dose of 300 mg/day.

For drug product development, the stability studies included the following configurations:

Bottle Size (cc)	Closure Type	Closure Size (mm)	Product Count	Product Strength
45	CR	24	2	All
120	CR	38	100	25, 50, 75, 100, 150, 200, 300
230	CR	45	100	150, 300
325	CR	38	500	25, 50, 75, 100
710	CT	43	500	150, 200, 225, 300

CR = Child resistant.
CT = Continuous thread.

The marketed drug product will use a 60 cc bottle size.

The Sponsor proposes an expiration dating period of three years for all strengths of pregabalin capsules packaged in ——— bottles and ___ blister packs when stored at 25°C. Based on the statistical analysis of real time stability data, the Agency grants a three year expiration period for the recommended market dosage strengths 25, 50, 75 and 100 mg capsules when packaged in the currently proposed 60 count, 60 cc ——— bottle configuration. However, for all other strengths (150, 200, 225, and 300 mg) and configurations a shelf life of two years is grantable at this time. Based on the accrual of additional real time stability data on the appropriate container/closer configurations, the Sponsor may extend the shelf life in the next annual report.

C. Basis for Approvability or Not-Approval Recommendation

This NDA application can be Approved from a CMC perspective, pending an Acceptable EES report. Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated.

Nevertheless, the Sponsor is expected to provide continued cooperation to resolve any problems that may be identified.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Sharon Kelly, Ph.D. / June 02, 2004
Ravi Harapanhalli, Ph.D. /
Lisa Malandro, Project Manager /

C. CC Block

11 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 3

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

/s/

Sharon Kelly
6/3/04 03:04:54 PM
CHEMIST

Ravi Harapanhalli
6/4/04 11:13:56 AM
CHEMIST

NDA 21-724

Lyrica (pregabalin) Capsules

C.P. Pharmaceuticals International

Thomas A. Broadbent, Ph.D.
Division of Neuropharmacological Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-724

2. REVIEW #: 2

3. REVIEW DATE: 26-MAY-2005

4. REVIEWER: Thomas A. Broadbent, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission NDA 21-446	30-OCT-2003
N-000 BC	17-FEB-2004
N-000 BC	20-APR-2004
N-000 BC	21-APR-2004
N-000 BC	22-APR-2004
N-000 BC	13-MAY-2004
N-000 BC	18-MAY-2004
N-000 BC	25-MAY-2004
NDA 21-446, CMC Review # 1	26-MAY-2004
NDA 21-446, CMC Review # 2	03-JUN-2004
NDA 21-446, TL-CMC Memorandum	04-JUN-2004
NDA 21-446, Division Director Review	29-JUL-2004
Telecon Memo	03-AUG-2004
Original Submission NDA 21-724	30-OCT-2003
N-000 BL	17-MAR-2004
N-000 BC	28-MAY-2004
N-000 BL	01-JUL-2004
N-000 BL	02-JUL-2004
N-000 BL	09-JUL-2004
NDA 21-724 CMC Review # 1	05-AUG-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N-000 BZ	11-MAR-2005
N-000 BL	18-MAR-2005

7. NAME & ADDRESS OF APPLICANT:

Name: C.P. Pharmaceuticals International C.V.
Address: 235 East Street 42nd Street
New York, NY 10017

U.S. Agent:
Name: Pfizer Global Research and Development
Address: 2800 Plymouth Road
Ann Arbor, MI 48105
Representative: Jonathan Parker, R.Ph., M.S.
Telephone: (734) 622-5377

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lyrica
b) Non-Proprietary Name (USAN): pregabalin
c) Code Name/#: CI-1008, PD 0144723
d) Chem. Type/Submission Priority:
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 USC Sec. 505 (b) (1)

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 25, 50, 75, 100, 150, 200, 225 & 300 mg

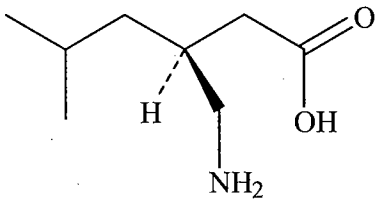
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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



(*S*)-3-(aminomethyl)-5-methylhexanoic acid
$C_8H_{17}NO_2$ Formula Weight 159.23

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					N/A		
					N/A		
					N/A		
					N/A		
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					N/A		
					N/A		
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					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
IND		Anticonvulsant Indication, CMC information
IND		
IND		
NDA	21-446	Neuropathic Pain of Diabetes, CMC provisions
NDA	21-723	Neuropathic Pain
NDA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	2-year retest schedule for drug substance	10-MAY-2004	Karl Lin
Biometrics	24 months expiration for 25, 50, 75 & 100 mg strengths; NMT 12 month extrapolation of stability data; annual stability testing insufficient	10-MAY-2004	Roswitha Kelly
EES	Acceptable	22-JUN-2004	S. Adams
Pharm/Tox	degradation product adequately qualified	07-APR-2004	Jerry Cott
Biopharmaceutics	Approvable Approval, with labeling recommendations	22-MAR-2004 02-JUL-2004	Sue-Chih Lee Veneeta Tandon
Methods Validation	No consult requested	--	--
ODS/DSRCS	Labeling Recommendations	03-JUN-2004	Jeanine Best
ODS/DMETS	Labeling revisions recommended & Proprietary name "Lyrica" acceptable Proprietary name "Lyrica" acceptable in reference to request from the Division of Neuropharmacological Drug Products	03-FEB-2004 20-MAY-2004	Kimberly Culley Alina Mahmud
EA	FONSI	25-FEB-2004	Florian Zielinski
Microbiology	N/A	--	--
Controlled Substance Staff	Abuse liability is found Schedule IV is recommended	31-MAR-2004	Katherine Bonson

Chemistry Review for NDA 21-617

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is recommended for the CMC perspective.

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

In negotiations for NDA 21-446, the sponsor committed to test the first three lots of pregabalin manufactured at the Ringaskiddy site using [redacted] See DACADP (HFD-170) telecon memo (6/01/04), CMC team leader's memo (6/04/04), and DNDC 2 Division Director's review (7/29/04). As of completion of this review, the [redacted] has not been adopted and the sponsor has not fulfilled the associated commitment. Lyrica Capsules produced from pregabalin manufactured with the proposed [redacted] process may not be marketed until the commitment is fulfilled.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Drug Substance:

Pregabalin, the drug substance for NDA 21-724, is provided by NDA 21-446. The CMC provisions have been reviewed by the CMC review team of the Division of Anesthetic, Critical Care and Addiction Drug Products (DACADP, HFD-170). Four CMC reviews have been posted.

Pregabalin is the established name (USAN & INN) of (*S*)-3-aminomethyl)-5-hexanoic acid. The molecular formula is $C_8H_{17}NO_2$. The CAS registry number is [148553-50-8]. Code names are CI-1008 and PD 0144723. The substance appears as a white to off-white crystalline solid. No characterization of odor has been given; odor is not expected, [redacted]

Drug Product:

NDA 21-724 (epilepsy) provides for Lyrica Capsules in strengths of 25, 50, 75, 100, 150, 200, 225, and 300 mg. The lead NDA, 21-446 (diabetic neuropathic pain), provides only the strengths 25, 50, 75 and 100 mg. Lyrica Capsules are formulated with two different blends for the fill material. Blend A is — pregabalin, — lactose monohydrate, — % corn starch and — % talc. Blend C is — % pregabalin, — % lactose monohydrate, — % corn starch and — % talc. Blend A is used for the 25 and 50 mg strengths. Blend C is used for all other strengths. No overage is used in manufacture of the capsules. All excipients are compliant with USP/NF monographs. The capsule shells are provided by — and comply with ONDC guidance concerning gelatin and BSE. The capsule shells are provided in sizes — and various binary color combinations of white and/or two shades of orange. The 50 mg strength is all white with a black band. Product specifications submitted in the amendment of 18-MAY-2004 were found acceptable. — is a degradation product as well as a DS impurity. The limit of the — in the drug product is — Identification method B (HPLC) was modified so that it could distinguish pregabalin from gabapentin, a related API of similar structure. The product will be manufactured at the Pfizer facility of Vega Baja, Puerto Rico. The Office of Compliance has evaluated this facility as acceptable.

The commercial product will be packaged in — bottles with a capsule count of 90. The strengths of 25, 50, 75, and 100 mg are packed in 60 cc bottles with — induction seals and — closures. The strengths of 150, 200, 225, 300 mg are packaged in — bottles with — induction seals and — closures. Physician samples of 30 capsules for 50, 75, 100 & 150 mg are packaged in — bottles with induction seals and — closures. Physician samples of 45 capsules for 50 mg are also packaged with induction seals and — closures. All bottle caps have a liner of — . The application also provides for professional samples in 6-capsule blister cards. Unit-dose blister packaging (a blister card of a single capsule) in packages of 100 for all strengths is provided for hospital use.

Expiration dating of 36 months for all strengths and presentations has been established.

The Controlled Substance Staff deems that Lyrica has a potential for abuse and has recommended that it be classified under Schedule IV as a controlled substance. Dr. Doug Throckmorton (Acting Deputy Director, CDER) has determined that Lyrica should be classified as Schedule V. DEA scheduling is pending.

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

Lyrica is indicated as adjunctive therapy in adults with partial seizures with [redacted] Pregabalin treatment starts with a dose of 150 mg per day and may be increased to 300 mg per day after 1 week, depending on response and tolerability. The maximum dose is 600 mg per day, which can be achieved after an additional week. Lyrica has also been proposed for other indications as provided in other applications, i.e. diabetic neuropathic pain (NDA 21-446), neuropathic pain [redacted] (NDA 21-723); [redacted]

NDA 21-446 Approved 12/30/04
NDA 21-723 Approved 12/30/04

C. Basis for Approvability or Not-Approval Recommendation

Approval for the CMC perspective is based upon the approval recommendation of the CMC review team of the Division of Anesthetics, Critical Care and Addiction Drug Products for NDA 21-446. CMC provisions of NDA 21-724 are referenced to NDA 21-446. This reviewer concurs with previous recommendation.

III. Administrative

A. Reviewer's Signature

Electronic signature in DFS

B. Endorsement Block

Chemist Name/Date: Thomas A. Broadbent – 26 May 2005
Chemistry Team Leader: Martha Heimann
Project Manager: Jackie Ware

C. CC Block

Chemist Name: Thomas A. Broadbent
Chemistry Team Leader: Martha Heimann
Project Manager: Jackie Ware

4 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-1

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/s/

Thomas Broadbent
6/1/05 10:45:12 AM
CHEMIST

Dr. Patel has initialled

Martha Heimann
6/1/05 11:19:23 AM
CHEMIST
Signed for Dr. Hasmukh B. Patel.

NDA 21-446

Lyrica (Pregabalin Capsules)

Pfizer Global Research & Development

Sharon L. Kelly
Anesthetic, Critical Care and Addiction
HFD 170

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-446

2. REVIEW #: 1

3. REVIEW DATE: December 18, 2003

4. REVIEWER: Sharon Kelly

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	30-OCT-2003
Amendment	17-FEB-2004
Amendment	03-MAR-2004
Amendment	21-APR-2004
Amendment	13-MAY-2004
Submission(s) Not Reviewed*	**Document Date**
Amendment	18-May-2004

*To be Reviewed in CMC Review #2

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Global Research and Development
Address:	2800 Plymouth Road Ann Arbor, Michigan 48105

Chemistry Assessment Section

Representative: Jonathon M. Parker, R.Ph., M.S.

Telephone: 734 - 622 - 5377

8. DRUG PRODUCT NAME/CODE/TYPE: LYRICA (pregabalin) Capsules

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

- Chem. Type: 1 New Molecular Entity
- Submission Priority: P Priority Review

9. LEGAL BASIS FOR SUBMISSION: 21 USC Sec. 505 (b)(1)

10. PHARMACOL. CATEGORY: Diabetic Neuropathy Agents

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 25, 50, 75, 100, 150, 200, 225, 300 mg

13. ROUTE OF ADMINISTRATION: Oral

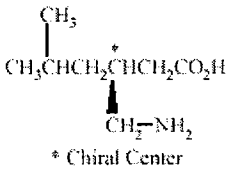
14. Rx/OTC DISPENSED: _XX_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

(S)-3-(aminomethyl)-5-methylhexanoic acid $C_8H_{17}NO_2$ Mol.Wt. 159.23



* Chiral Center

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

	4	N/A		
	4	N/A		
	4	N/A		

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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
IND		CI-1008 Capsules Anti Convulsant
IND		
IND		
NDA	21-723	Pregabalin Capsules Neuropathic pain associated
NDA	21-724	Pregabalin Capsules Epilepsy
NDA		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

Chemistry Assessment Section

Biometrics	2-year retest schedule for drug substance	10-MAY-2004	Karl K. Lin, Ph.D.
Biometrics	Extrapolation of no more than 12 months beyond amount of actual stability data for drug product: Two year shelf life. Yearly interval stability testing of annual batches insufficient.	10-MAY-2004	Roswitha Kelly, MS
EES	Pending, May 19, 2004		
Pharm/Tox	[redacted] degradation product adequately qualified	07-APR-2004	Jerry Cott, Ph.D.
Biopharm	preNDA Meeting: Human Pharmacokinetics and Bio - availability - Dissolution Profile	07-JUN-2000	Meeting Minutes Finalized 23-JAN-2001
Methods Validation	Pending Approval		
ODS / DMETS	Labeling revisions. Proprietary name Lyrica™ acceptable	03-FEB-2004	Kimberly Culley, RPh
EA	FONSI Recommended	25-FEB-2004	Florian Zielinski, Ph.D.
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-446

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA application can be Approved from a chemistry review perspective, pending an Acceptable EES report. In addition, there are two Comparability Protocols included in this application that are acceptable if further commitments are agreed to by the Sponsor. The Sponsor has not yet responded to an Information Request letter. However, in the 13-May-2004 Amendment, a major deficiency was addressed. The Sponsor demonstrated that a drug substance Specification for was not necessary.

A two year shelf life is grantable for the drug substance when stored at the recommended conditions. Data from additional batches is needed to support the Sponsor's proposal of a test period.

A three year shelf life is grantable for the drug product when stored at the recommended conditions only for the currently proposed configuration ie bottles containing 60 capsules for the 25 mg, 50 mg, 75 mg, and 100 mg capsule strengths For the addition of new product configurations or dosage strengths, the expiry dating period will have to be supported by additional real time stability data that is ongoing.

The EES report 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)

It is proposed that pregabalin capsules should be indicated for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and, as adjunctive therapy, for the treatment of and adult patients

with partial seizures. The indication for this NDA and for the purposes of this chemistry review is neuropathic pain associated with DPN.

Pregabalin was developed as opaque hard gelatin shell capsules in dosage strengths of 25, 50, 75, 100, 150, 200, 225, and 300 mg. The marketed dosage strengths will be 25, 50, 75 mg and 100 mg capsules. To avoid any possible patient or pharmacist confusion, the capsules are colored, and imprinted with black ink to indicate the strength and product code, as follows:

Strength (mg)	Capsule Size	Capsule Color (Body/Cap)
25	4	White/white
50	3	White (with black ink band)/white
75	4	White/orange
100	3	Orange/orange
150	2	White/white
200	1	Light orange/light orange
225	1	White/light orange
300	0	White/orange

The drug product is packaged into either bottles or blisters. The marketed configuration will be the bottle. However, during development, bottle configurations were in the range The configurations include seals and both child-resistant and nonchild-resistant closures, and identical liner material. The blister system is made of a blister with a foil backing.

There is no processing or sterilization needed for pregabalin manufacture. The excipient, lactose monohydrate, and the bovine gelatin used in capsule shells, are in full compliance with the Guidance "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-regulated Products for Human Use".

The Sponsor proposes a retest period for pregabalin drug substance when packaged in when stored at room temperature, or The drug substance , although not light sensitive, will be protected from light during storage according to the usual precautions. The stability data is evaluated in the Chemistry Assessment, drug substance section of this review. Statistical analysis of the data supports only a 2-year retest period for the drug substance.

The physicochemical and biological properties have been adequately characterized and are shown not to influence batch reproducibility, product performance and/or drug product quality. The impurity levels are sufficiently characterized and controlled by characteristics of the drug substance. The drug substance synthesis employs procedures that are adequately documented.

Pregabalin is [redacted] It is [redacted] soluble in water. At room temperature the saturation solubility of Pregabalin in aqueous media is [redacted] mg/ml in the pH range [redacted] The compound is classified as highly soluble and highly permeable under the Biopharmaceutical Classification System (BCS). Data demonstrates that the drug product is almost completely dissolved within [redacted]; and is independent of API particle size. The manufacture and performance of the drug product has been demonstrated over a wide range of drug substance particle size, due, in part, to the evolution of process and [redacted] parameters at three manufacturing sites.

The drug substance IUPAC designation is (S)-3-(aminomethyl)-5-methylhexanoic acid. The synthetic route for pregabalin employs classical resolution [redacted] of the racemic amino acid to produce the desired (S)-enantiomer. If there is inadequate removal of the (R)-enantiomer, the amount can be reduced by applying the [redacted]

The synthetic scheme employs [redacted] a Class II solvent according to ICH Q3C. For anticipated doses of [redacted] of pregabalin, the [redacted] is controlled at a sufficient level, [redacted] (ICH Q3C recommends [redacted]. The scheme also employs isopropyl alcohol, which is not listed in ICH Q3C, but controls are established at [redacted] This solvent most closely resembles Class III solvents, and according to ICH Q3C, they should be limited by GMP or other quality-based requirements. Available data indicate amounts of 50 mg per day or less (corresponding to [redacted] would be acceptable without justification.

The drug product manufacturing process attributes (critical parameters) have been adequately examined and have been shown not to influence batch reproducibility, product performance and/or quality. The manufacturing process consists of [redacted] The excipients are lactose monohydrate, corn starch, and talc.

Pregabalin capsule composition has remained unchanged throughout development and commercial introduction. Changes in capsule shell color and size were made to accommodate blinding and market image aesthetics. Consequently, three different powder blends, designated as A, B, and C have been used in clinical studies. The bioequivalence of clinical formulations was demonstrated *in vitro* and a biowaiver was granted as documented in the preNDA meeting minutes of 07-JUN-2000.

The proposed commercial capsule products are filled with 1 of 2 powder blend formulations. The Series A powder blend contains [redacted] Pregabalin by weight and is used to produce 25- and 50-mg capsule strengths; Series C powder blend contains [redacted] Pregabalin by weight and is used to produce 75-, 100-, 150-, 200-, 225-, and 300-mg capsule strengths. Note the 150- and higher capsule strengths are not being proposed for marketing at this time.

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

Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). It interacts with an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin. Binding to the α_2-δ site is
required for analgesic, anticonvulsant and anxiolytic activity in animal models. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.

The Agency agrees to 25, 50, 75 or 100 mg capsule strengths to be given in three divided doses, to a maximum recommended dose of 300 mg/day.

For drug product development, the stability studies included the following configurations:

Bottle Size (cc)	Closure Type	Closure Size (mm)	Product Count	Product Strength
45	CR	24	2	All
120	CR	38	100	25, 50, 75, 100, 150, 200, 300
230	CR	45	100	150, 300
325	CR	38	500	25, 50, 75, 100
710	CT	43	500	150, 200, 225, 300

CR = Child resistant.
CT = Continuous thread.

The marketed drug product will use a 60 cc bottle size.

The Sponsor proposes an expiration dating period of three years for all strengths of pregabalin capsules packaged in ~ bottles and ~ blister packs when stored at 25°C. Based on the statistical analysis of real time stability data, the Agency grants a two year expiration period for the recommended market dosage strengths 25, 50, 75 and 100 mg capsules.

C. Basis for Approvability or Not-Approval Recommendation

This NDA application can be Approved from a CMC perspective, pending an Acceptable EES report. Minor Chemistry issues and a resolution on the acceptability of the Comparability Protocol for the new drug substance synthetic scheme are pending. An Information Request letter was sent to the Sponsor. It is expected that the information will be submitted by the Sponsor and reviewed before a decision is made by the Agency. In the event that there are any unresolved issues pertaining to the Comparability Protocol, the Sponsor should be asked to withdraw the Comparability Protocol from the NDA.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Sharon Kelly, Ph.D. / May 24, 2004
Ravi Harapanhalli, Ph.D. /
Lisa Malandro, Project Manager /

C. CC Block

171 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1A

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/s/

Sharon Kelly
5/26/04 10:53:04 AM
CHEMIST

Ravi Harapanhalli
5/26/04 03:46:59 PM
CHEMIST