

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-488

CHEMISTRY REVIEW(S)

NDA 22-488

**Lyrica
(pregabalin) oral solution**

C.P. Pharmaceuticals International C.V.

Chemistry Review #2

**John C. Hill, Ph.D.
ONDQA/DPMA-1 and OND/ODE II/DAARP**

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Chemistry Review Data Sheet

1. NDA #22-488
2. REVIEW #2
3. REVIEW DATE: 05-NOV-2009
4. REVIEWER: John C. Hill, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

IND 49,393 (Epilepsy)	8-Dec-95
IND 53,763 (Pain)	24-July-97
(b) (4)	8-Oct-97
IND 66,902 (Fibromyalgia)	27-May-04
IND 76,815 (Liquid / epilepsy)	21-Dec-06
(b) (4)	10-Jan-08
NDA 21-446 (Neuropathic Pain – DPN)	30-Oct-03
NDA 21-723* (Neuropathic Pain – PHN)	30-Oct-03
NDA 21-724* (Epilepsy)	30-Oct-03
(b) (4)	30-Oct-03
NDA 21-446/S-010 (Fibromyalgia)	20-Dec-06
22-488-000 (Original NDA Application)	04-MAR-2009
BC (Response to deficiencies communicated in filing letter)	22-MAY-2009
BL (Revised labeling/SPL)	29-MAY-2009

*NDAs 21-723, 21-724 and (b) (4) are administrative NDAs attached to NDA 21-446. With the approval of the Neuropathic Pain – PHN and Adjunctive Epilepsy indications, NDAs 21- 723 and 21-724 are subsumed within NDA 21-446.

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
BC (Response to DR letter)	30-SEP-2009
Quality memo to file	05-NOV-2009

7. NAME & ADDRESS OF APPLICANT:



Chemistry Review Data Sheet

Name: C.P Pharmaceuticals International C.V.
c/o Pfizer Inc.
Address: 235 East 42nd Street
New York, NY 10017
Att: David Reid, Manager, C.P. Pharmaceuticals Int'l C.V.
Pfizer Inc.
Representative: 50 Pequot Avenue
New London, CT 06320
Telephone: (212) 573-4471

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: LYRICA
- b) Non-Proprietary Name (USAN): Pregabalin
- c) Code Name/# (ONDC only): CI-1008, A008, PD 0144723
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Neuropathic Pain, Epilepsy and Management of Fibromyalgia

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 20 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

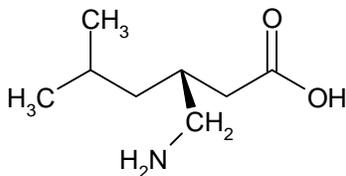
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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



Name: (S)-3-(aminomethyl)-5-methylhexanoic acid

Molecular Formula: C₈H₁₇NO₂

Molecular Weight: 159.23

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	4	Adequate		LOA: 03-SEP-2008
	III			4	Adequate		LOA: 03-OCT-2008
	III			4	Adequate		23-SEP-2008
	III			4	Adequate		LOA: 25-SEP-2008
	III			4	Adequate		LOA: 23-SEP-2008
	III			4	Adequate		LOA: 24-SEP-2008

(b) (4)

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

Chemistry Review Data Sheet

- 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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	06-APR-2009	E. Johnson
Pharm/Tox	Acceptable (Oral confirmation)	Pending	K. Young/A. Wasserman
Biopharm	Acceptable	05-Jun-2009	H. Mahayni
Methods Validation	Not Required	05-JUN-2009	J. Hill
EA	Acceptable	05-JUN-2009	J. Hill

OGD:

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes
 No If no, explain reason(s) below:

The Chemistry Review for NDA 22-488

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and control perspective, this application can be approved.

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

None

II. Summary of Chemistry Assessments

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

Drug Product

Lyrica oral solution, 20 mg/mL is a new oral formulation of pregabalin (currently approved as a hard capsule dosage form for oral use (25 to 300 mg) designed to be given orally with or without food. The referenced approved NDA # is 21-466.

The oral solution concentration was selected at 20 mg/mL for dosing flexibility. The daily dose volume for patients is expected to be up to 30 mL (600 mg pregabalin).

Lyrica oral solution, 20 mg/mL is a clear, colorless, and flavored solution contained in a 500-mL (16 fluid ounce) white high-density polyethylene bottle with a polyethylene-lined, child-resistant closure. A sweetening agent (sucralose) and flavor (artificial strawberry) are added to mask the bitter taste of pregabalin. The solution is buffered to approximately pH 6.1 with phosphate buffer. The formulation includes a preservative system consisting of methylparaben and propylparaben providing adequate microbiological stability of the formulation throughout its shelf life and intended use life. Accelerated stability screens demonstrated the compatibility of the formulation excipients with the pregabalin drug substance.

Lyrica oral solution, 20 mg/mL is initially intended to be used for adult patients who may require a liquid formulation (e.g., for patients who have difficulty swallowing capsules) (b) (4). Indications and dosage will be exactly the same as for the currently approved capsules. In the United States (US), pregabalin is currently approved as Lyrica® for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, epilepsy (adjunctive therapy for adult patients with partial onset seizures), and fibromyalgia.

The provided stability data support storage of the drug product for 24 months at or below the ICH alternative storage conditions of 30°C +/- 2°C/35% Relative Humidity (RH) +/- 5% and a 45 day use period for opened bottles when stored at or below 30°C +/- 2°C/35% RH +/- 5%

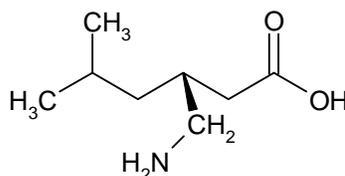
Drug Substance (from review of NDA 21-446)

Executive Summary Section

Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). It interacts with an auxiliary subunit ($\alpha 2\text{-}\delta$ protein) of voltage-gated calcium channels in the central nervous system, potentially displacing [^3H]-gabapentin. Binding to the $\alpha 2\text{-}\delta$ 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.

Pregabalin is crystalline and exists in single morphic form. It is not solvated. It is nonhygroscopic, thermally stable, and soluble in water. At room temperature, the saturation solubility of Pregabalin in aqueous media is >30 mg/ml in the pH range 1 to 13. 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 (b) (4) 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 (b) (4) parameters at three manufacturing sites.

The structure of the pregabalin drug substance is illustrated as follows.



The molecular formula is: $\text{C}_8\text{H}_{17}\text{NO}_2$

The molecular weight is: 159.23

The drug substance IUPAC designation is (S)-3-(aminomethyl)-5-methylhexanoic acid. The synthetic route for pregabalin employs classical resolution (b) (4) 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 (b) (4) recrystallization from IPA/water. The racemate stage is a control point in the synthetic scheme.

The synthetic scheme employs (b) (4), a Class II solvent according to ICH Q3C. For anticipated doses of (b) (4) of pregabalin, the (b) (4) is controlled at a sufficient level (b) (4) (ICH Q3C recommends ≤ 720 ppm). The scheme also employs isopropyl alcohol, which is not listed in ICH Q3C, but controls are established at (b) (4). 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 (b) (4)) would be acceptable without justification.

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

Lyrica oral solution, 20 mg/mL is designed to be given orally with or without food.

C. Basis for Approvability or Not-Approval Recommendation

This NDA contains adequate and appropriated descriptions of the manufacture, characterization, control and quality of the Lyrica oral solution, 20 mg/mL. Sufficient stability data have been provided to support an expiry period of 24 months at or below the ICH alternative storage

Executive Summary Section

conditions of 30°C +/- 2°C/35% RH +/- 5% and a 45 day use period for opened bottles when stored at or below 30°C +/- 2°C/35% RH +/- 5%.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

John C. Hill, Ph.d./Date: as noted in electronic signature block

Prasad Peri, Ph.D., Acting Chief, Branch II, DPMA I, ONDQA/Date: as noted in electronic signature block

C. CC Block

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22488

ORIG-1

PFIZER CHEMICAL
CORP

LYRICA (PREGABALIN)

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

/s/

JOHN C HILL
11/06/2009

PRASAD PERI
11/06/2009

NDA 22-488

**Lyrica
(pregabalin) oral solution**

C.P. Pharmaceuticals International C.V.

**John C. Hill, Ph.D.
ONDQA/DPMA-1 and OND/ODE II/DAARP**

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Chemistry Review Data Sheet

1. NDA #22-488
2. REVIEW #1
3. REVIEW DATE: 31-JUL-2009
4. REVIEWER: John C. Hill, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

IND 49,393 (Epilepsy)	8-Dec-95
IND 53,763 (Pain)	24-July-97
(b) (4)	8-Oct-97
IND 66,902 (Fibromyalgia)	27-May-04
IND 76,815 (Liquid / epilepsy)	21-Dec-06
(b) (4)	10-Jan-08
NDA 21-446 (Neuropathic Pain – DPN)	30-Oct-03
NDA 21-723* (Neuropathic Pain – PHN)	30-Oct-03
NDA 21-724* (Epilepsy)	30-Oct-03
(b) (4)	30-Oct-03
NDA 21-446/S-010 (Fibromyalgia)	20-Dec-06

*NDAs 21-723, 21-724 and (b) (4) are administrative NDAs attached to NDA 21-446. With the approval of the Neuropathic Pain – PHN and Adjunctive Epilepsy indications, NDAs 21- 723 and 21-724 are subsumed within NDA 21-446.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

22-488-000 (Original NDA Application)	04-MAR-2009
BC (Response to deficiencies communicated in filing letter)	22-MAY-2009
BL (Revised labeling/SPL)	29-MAY-2009

7. NAME & ADDRESS OF APPLICANT:

Name:

C.P Pharmaceuticals International C.V.

Chemistry Review Data Sheet

Address: c/o Pfizer Inc.
235 East 42nd Street
New York, NY 10017
Att: David Reid, Manager, C.P. Pharmaceuticals Int'l C.V.
Pfizer Inc.
Representative: 50 Pequot Avenue
New London, CT 06320
Telephone: (212) 573-4471

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: LYRICA
- b) Non-Proprietary Name (USAN): Pregabalin
- c) Code Name/# (ONDC only): CI-1008, A008, PD 0144723
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Neuropathic Pain, Epilepsy and Management of Fibromyalgia

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 20 mg/mL

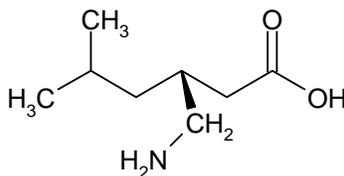
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)
 SPOTS product – Form Completed
 Not a SPOTS product

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

Chemistry Review Data Sheet



Name: (S)-3-(aminomethyl)-5-methylhexanoic acid

Molecular Formula: C₈H₁₇NO₂

Molecular Weight: 159.23

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	4	Adequate		LOA: 03-SEP-2008
	III			4	Adequate		LOA: 03-OCT-2008
	III			4	Adequate		23-SEP-2008
	III			4	Adequate		LOA: 25-SEP-2008
	III			4	Adequate		LOA: 23-SEP-2008
	III			4	Adequate		LOA: 24-SEP-2008

(b) (4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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5 – Authority to reference not granted

6 – DMF not available

Chemistry Review Data Sheet

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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	06-APR-2009	E. Johnson
Pharm/Tox			
Biopharm	Acceptable	05-Jun-2009	H. Mahayni
LNC			
Methods Validation	Not Required	05-JUN-2009	J. Hill
OPDRA			
EA	Adequate	05-JUN-2009	J. Hill
Microbiology			

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	X		
EES	X		
Methods Validation	X		
Labeling	X		
Bioequivalence	X		
EA	X		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes
 ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-488

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and control perspective, the application is approvable pending the followings:

- Adequate responses to outstanding CMC deficiencies,
- Adequate responses to outstanding consultative review requests.

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

None

II. Summary of Chemistry Assessments

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

Drug Product

Lyrica oral solution, 20 mg/mL is a new oral formulation of pregabalin (currently approved as a hard capsule dosage form for oral use (25 to 300 mg). The referenced approved NDA # is 21-466.

The oral solution concentration was selected at 20 mg/mL for dosing flexibility. The daily dose volume for patients is expected to be up to 30 mL (600 mg pregabalin).

Lyrica oral solution, 20 mg/mL is a clear, colorless, and flavored solution contained in a 500-mL (16 fluid ounce) white high-density polyethylene bottle with a polyethylene-lined closure. A sweetening agent (sucralose) and flavor (artificial strawberry) are added to mask the bitter taste of pregabalin. The solution is buffered to approximately pH 6.1 with phosphate buffer. The formulation includes a preservative system consisting of methylparaben and propylparaben providing adequate microbiological stability of the formulation throughout its shelf life and intended use life. Accelerated stability screens demonstrated the compatibility of the formulation excipients with the pregabalin drug substance.

Lyrica oral solution, 20 mg/mL is initially intended to be used for adult patients who may require a liquid formulation (e.g., for patients who have difficulty swallowing capsules) (b) (4)

Indications and dosage will be exactly the same as for the currently approved capsules. In the United States (US), pregabalin is currently approved as Lyrica® for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, epilepsy (adjunctive therapy for adult patients with partial onset seizures), and fibromyalgia.

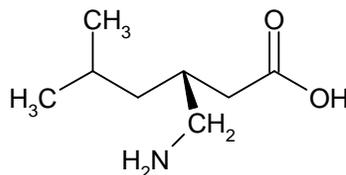
The provided stability data support storage of the drug product for 24 months at or below the ICH alternative storage conditions of 30°C +/- 2°C/35% RH +/- 5% and a 45 day use period for opened bottles when stored at or below 30°C +/- 2°C/35% RH +/- 5%

Executive Summary Section

Drug Substance (from review of NDA 21-446)

Pregabalin is crystalline and exists in single morphic form. It is not solvated. It is nonhygroscopic, thermally stable, and soluble in water. At room temperature, the saturation solubility of Pregabalin in aqueous media is >30 mg/ml in the pH range 1 to 13. 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 (b) (4)s 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 (b) (4) parameters at three manufacturing sites.

The structure of the pregabalin drug substance is illustrated as follows.



The molecular formula is: C₈H₁₇NO₂

The molecular weight is: 159.23

The drug substance IUPAC designation is (S)-3-(aminomethyl)-5-methylhexanoic acid. The synthetic route for pregabalin employs classical resolution (b) (4) 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 (b) (4) recrystallization from IPA/water. The racemate stage is a control point in the synthetic scheme.

The synthetic scheme employs (b) (4), a Class II solvent according to ICH Q3C. For anticipated doses of (b) (4) of pregabalin, the (b) (4) is controlled at a sufficient level, (b) (4) (ICH Q3C recommends ≤ 720 ppm). The scheme also employs isopropyl alcohol, which is not listed in ICH Q3C, but controls are established at (b) (4). 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 (b) (4)) would be acceptable without justification.

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 (α2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [3H]-gabapentin. Binding to the α2-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.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is not approvable from a CMC perspective. The following outstanding CMC deficiencies remain to be addressed:

Executive Summary Section

- Adequate responses to communicated CMC deficiencies,
- Adequate responses from outstanding consultative review requests.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

John C. Hill, Ph.d./Date: as noted in electronic signature block

Ali Al-Hakim, Ph.D., Chief, Branch II, DPMA I, ONDQA/Date: as noted in electronic signature block

C. CC Block

52 Page(s) has been Withheld in Full immediately following this page as B4 (CCI/TS)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22488	ORIG 1		LYRICA (PREGABALIN)
NDA 22488	ORIG 1		LYRICA (PREGABALIN)
NDA 22488	ORIG 1		LYRICA (PREGABALIN)

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

/s/

JOHN C HILL
08/04/2009

ALI H AL HAKIM
08/04/2009

Initial Quality Assessment
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

OND Division:	Anesthesia, Analgesia and Rheumatology	
NDA:	22-488	
Applicant:	Pfizer	
Stamp date:	March 4, 2009	
PDUFA Date:	January 4, 2010	
Trademark:	Lyrica®	
Established Name:	Pregabalin oral solution	
Dosage Form:	Oral solution, 20 mg/ml	
Route of Administration:	Oral	
Indication:	Management of pain; all approved indications for pregabalin capsules	
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	<u>√</u>	_____
Comments for 74-Day Letter:	<u>√</u>	_____

Summary, Critical Issues and Comments

A. Summary

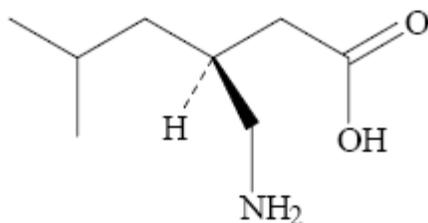
Pregabalin is a γ -aminobutyric acid analog and a schedule V controlled substance. Pregabalin has analgesic, anxiolytic, and anticonvulsant activity, which is thought to be mediated through selective binding to the $\alpha 2$ - δ subunit of voltage-gated calcium channels in the central nervous system. Pregabalin has been approved as Lyrica® capsules (25 – 300 mg), for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, epilepsy (adjunctive therapy for adult patients with partial onset seizures), and fibromyalgia. This new formulation, 20 mg/mL oral solution, is intended for adult patients who may have difficulty swallowing capsules. The applicant submitted the current formulation with no additional non-clinical or clinical data, based on the biowaiver agreements with FDA (Meeting Minutes in Module 1.6.3). No drug substance data are included in the application, but they are cross-referenced to NDA 21-466.

The drug product is formulated as a multi-dose oral aqueous solution with sweetener, flavorant at a pH of 6.1, and an antimicrobial preservative system in WHDPE bottles with PE-lined closures. Based on 12-month real time stability data, and statistical analysis evaluation, a 24-month shelf-life is proposed for the product.

B. Review, Comments and Recommendations

Drug Substance Pregabalin

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight



(S)-3-(aminomethyl)-5-methylhexanoic acid

Molecular formula: C₈H₁₇O₂

Molecular weight: 159.23

Pregabalin is manufactured by Pfizer, in Ringaskiddy, and Little Island, County Cork Ireland and Pfizer Asia Pacifico in Singapore. The following CMC information is summarized from the CMC reviews of the cross-referenced approved NDAs. Only one crystal form is known. The compound has one stereogenic center. The *S* configuration has been established by single crystal X-ray diffraction of the *S*-mandelate salt. Optical rotation α_D^{25} is of low magnitude and thus is not useful for analysis. Enantiomeric purity of the drug substance is determined by HPLC analysis of its derivative of condensation with Marfey's reagent. Since this is a solution formulation, the solid state properties of the drug substance do not impact manufacturability and performance of the new formulation. Significant racemization of the drug substance has not been observed under normal stability conditions and stress testing. Sensitivity to light was not observed in a photostability study conducted along ICH guidelines. The α_D^{25} and the enantiomer of pregabalin (limit α_D^{25}) are the only related substances specified by the regulatory drug substance specifications. A retest period of α_D^{25} for the drug substance has been established. Note that in negotiations for NDA 21-466, the sponsor has committed to test the first three lots of pregabalin manufactured at the Ringaskiddy site for α_D^{25} , and if present, to add a limit of α_D^{25} for this impurity to the drug substance specifications. The applicant stated that these data were

submitted in the Annual Report of 2006 (M1). The annual report should be evaluated and verified accordingly. In addition, a comparability protocol for an alternate synthesis of the drug substance via the (b) (4) has been approved in NDA 21-466. In the alternate synthesis, the (b) (4) is used for (b) (4). Pfizer has agreed to adopt additional specifications for drug substance manufactured by the alternate route: (b) (4) : NMT (b) (4) (b) (4) NMT: (b) (4). Additional specifications may be established after assessment of test results, and the pregabalin synthesis will be implemented by a CBE-30 supplement. The applicant should be asked to submit the summary of updated drug substance specifications to the current NDA.

Table 1 – Specifications for Pregabalin (original submission, NDA 21-446)

Test	Method	Acceptance Criterion
Description	Visual	White to off-white solid
Identification A	IR	Agrees with reference standard spectrum
Identification B	HPLC	Retention time agrees with that of reference standard
Assay	HPLC	98.0% to 102.0% (w/w)
Impurities	HPLC	(b) (4)
Water Content	KF per USP <921> Method Ia ②	(b) (4)
Heavy Metals	USP <231> Method II③	(b) (4)
Residue on Ignition	USP <281> ④	(b) (4)
Residual Solvents	GC	(b) (4)
Bulk Density	USP <616> ⑤	(b) (4)

- ② This method is equivalent to Ph. Eur. 2.5.12 Method A.
- ③ This method is equivalent to Ph. Eur. 2.4.8 Method C.
- ④ This method is equivalent to Ph. Eur. 2.2.14.
- ⑤ This method is equivalent to Ph. Eur. 2.2.42.

Figure 1 – Specified Impurity

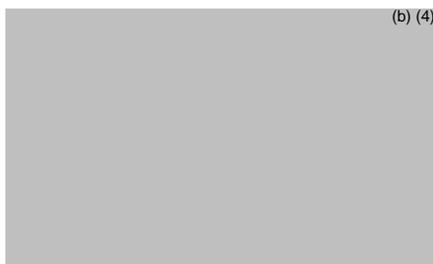


Figure 2 – Specified Impurity



Drug product

The drug product is a clear aqueous solution for oral administration. The product is filled into 16 fluid oz (473 mL nominal fill) white HDPE bottle with a PE-lined closure. The solution contains a sweetening agent (sucralose) and artificial strawberry flavor, to mask the bitter taste of pregabalin. The multi-dose solution is buffered to 6.1 and contains methylparaben and propylparaben preservative system.

Quantitative composition for pregabalin oral solution is provided below.

Table 2. Quantitative composition of pregabalin oral solution, 20 mg/ml

Component	Function	Reference to Standards ¹	Unit Formula (mg/mL)
Pregabalin	Active	In house standard	20.0
Methylparaben (methyl parahydroxybenzoate)	Preservative	NF ² or Ph. Eur. ³	(b) (4)
Propylparaben (propyl parahydroxybenzoate)	Preservative	NF or Ph. Eur.	
Monobasic sodium phosphate anhydrous	(b) (4)	USP ⁴	
Dibasic sodium phosphate anhydrous		USP or Ph. Eur.	
Sucralose	Sweetener	NF	
Artificial Strawberry Flavor #11545	Flavor	N/A ⁵	
Purified Water	(b) (4)	USP or Ph. Eur.	

¹ Relevant compendial grade testing will be used in each region (for example, USP/NF for US region, Ph. Eur for EU region)

² NF = National Formulary

³ Ph. Eur. = European Pharmacopoeia

⁴ USP = United States Pharmacopoeia

⁵ N/A = Not Applicable

⁶ (b) (4)

Manufacturing Process:

The proposed commercial manufacturer is Pfizer Inc., in Kalamazoo, MI. This facility performs also release, stability testing, and packaging of the drug product. The commercial batch size is (b) (4). Batch formula is shown in Table 3, below.

Table 3. Batch Formula

Component	Function	Reference to Standards ¹	Quantity per Batch
Pregabalin (API)	Active	In house standard	(b) (4)
Methylparaben (methyl parahydroxybenzoate)	Preservative	NF ² or Ph. Eur. ³	
Propylparaben (propyl parahydroxybenzoate)	Preservative	NF or Ph. Eur.	
Monobasic Sodium Phosphate, Anhydrous	(b) (4)	USP ⁴	
Dibasic Sodium Phosphate, Anhydrous		USP or Ph. Eur.	
Sucralose	Sweetener	NF	
Artificial Strawberry #11545	Flavor	N/A ⁵	
Purified Water (Total)	(b) (4)	USP or Ph. Eur.	

The manufacturing process and process controls comprise of standard operations of compounding and filling for liquid products and are described in sufficient detail.

The flow chart of the manufacturing process is shown below:
Flow Chart of the Manufacturing Process

(b) (4)

Process validation: The commercial process will be validated prior to commercial launch.

Pharmaceutical Development:

The drug substance, pregabalin, has been characterized in the previously approved NDAs. Since the drug product is formulated as a solution, the particle size, morphic form and other solid state properties of the drug substance are not expected to impact the manufacturability and bioavailability of the drug product. The two developmental formulations, one of which was used in Phase 1 clinical trial, have been included in the submission. There are no critical excipients or attributes of the drug product. The applicant optimized the use of a sweetener and flavorant to mask the bitter taste of pregabalin and the pH range (5.9 – 6.1) for optimal stability. Finally, the applicant utilized a well-known preservative system and tested its antimicrobial preservative effectiveness as per USP<51>. Degradation and stability studies determined the presence of a degradant, (b) (4), formed from the (b) (4); however its levels in the samples were observed below (b) (4) (see figure below). For the non-compendial excipient, artificial strawberry flavor #11545, the applicant provided specifications and claimed that is not a novel excipient. The daily exposure to the artificial flavorant is 30 mg, based on a 30 ml intake (see Table 4, below). This claim should be assessed in consultation with the toxicology division. The composition, CFR compliance of components and suitability of the proposed specifications should be assessed. The manufacturing process was scaled up from (b) (4) (Phase 1) to (b) (4) (primary stability batches). The proposed commercial scale is (b) (4). The applicant claimed comparability of the equipment and processes used and this should be assessed.

Suitability of the container closure system was based on stability data and a stressed study; no specific leachables/extractables evaluation was performed. Additional information and justification regarding leachables/extractables should be requested from the applicant.

Table 4. Daily exposure to pregabalin components

Component	Maximum Daily Intake per 30 mL/day Dosing (mg)
Pregabalin	600
Methylparaben	39.0
Propylparaben	4.89
Monobasic sodium phosphate anhydrous	97.5
Dibasic sodium phosphate anhydrous	12.5
Sucralose	75.0
Artificial Strawberry Flavor #11545	30.0

Figure 3.2.P.5.5-2. Structure of (b) (4)



Chemical Name:

(b) (4)

Drug Product Specifications:

Test Name	Test Method	Test Method Reference Number	Acceptance Criteria
Appearance	Visual inspection	I 2.02	Clear colorless solution
Identification:			
Identity	RP-HPLC	TM-00-0023A	Retention time conforms to reference standard
Identity	NIR	TM-00-0025A	Spectrum obtained for the solution is identical to that for the library
Assay:			
Assay	RP- HPLC	TM-00-0023A	(b) (4)
Impurities:			
(b) (4)	RP- HPLC	TM-00-0023A	(b) (4)
	RP- HPLC	TM-00-0023A	
	RP- HPLC	TM-00-0023A	
Preservative Content:			
Methylparaben	RP-HPLC	TM-00-0024A	(b) (4)
Propylparaben	RP-HPLC	TM-00-0024A	
Microbial Limits:			
Total Aerobic Count	Microbiologic	USP <61>	(b) (4)
Yeast and Mold	Microbiologic	USP <61>	
<i>E. coli</i>	Microbiologic	USP <62>	
Additional Tests			
pH at 25°C	pH	USP <791>	

Analytical methods are based on compendial procedures with the exception of: Identification (HPLC and NIR), assay (HPLC), impurities (HPLC) and preservative content (HPLC). Methods Validation, according to ICH Q2A, is provided in the submission and should be assessed.

Batch analysis data:

Batch analysis data are included for four drug product batches at the (b) (4) scale. Note, that levels of individual and total impurities at release are (b) (4) for all four batches.

NDA batches:

39RDY, 22RFA, 21RFA, K7288

Container Closure System:

Bottle/Closure System			
Strength	Nominal Fill	Bottle Size	Closure Size
20 mg/mL	16 fl. oz. (473 mL)	500 mL	28 mm

Summary of the components, suppliers and DMF references is included in the NDA. However, chemical composition and specifications of packaging components have not been included in the NDA but referenced to the corresponding DMFs. The applicant indicated that the HDPE containers were tested for extractables as per USP<661>. These data have not been included in the application, thus should be verified in the corresponding DMFs. In addition, a leachables evaluation has not been provided and should be requested from the applicant. Suitability of the container/closure system should be assessed.

The applicant stated that: “Stability studies were performed using closures with a (b) (4)

The applicant should specify the blowing agent in their proposed commercial liner and demonstrate comparability of the two proposed liners with respect to leachables/extractables evaluation in the drug product. Note, that the container/closure used in the “purposeful degradation study” conducted by the applicant at 70°C, was glass vials sealed with Teflon lined caps.

Stability:

Stability testing of the product has been performed at 30°C/35% RH and 40°C/25% RH. The stability studies included photostability, thermal cycling, and an in-use stability study at 30°C for 45 days. However, horizontal and inverted configurations have not been included. Stability protocols are provided. Summary of the stability data on the registration batches, **39RDY, 22RFA, 21RFA** is provided in the NDA. No significant trends have been observed on stability, individual and total impurities/degradants remained (b) (4). The applicant proposed 24 months expiration dating based on 12-month real time stability data on registration batches, and statistical evaluation of the stability data. An-in use expiration dating of (b) (4) has been proposed based on the 45-day study at 30°C. The proposed expiration dating and in-use shelf life should be assessed. A justification for the storage conditions used should be requested from the applicant.

Labeling

Labeling information on the container labels and packaging insert should be assessed with respect to CMC information. SPL labeling has been included in M1.

C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. The current drug substance specifications should be verified. The applicant stated (M1) that results regarding the impurity [REDACTED] (b) (4) were submitted in the 2006 AR report to NDA 21-466. This should be verified and the results should be assessed.
2. Components, specifications and amount of the non-pharmacopeial excipient artificial strawberry flavor in consultation with the Toxicology division.
2. Hold times of intermediates during the manufacturing process should be assessed.
3. Methods Validation for the non-compendial methods for the drug product.
4. Specifications for drug product impurities/degradants in consultation with the Toxicology division.
5. Suitability of the antimicrobial preservative system and evaluation of its antimicrobial preservative effectiveness.
6. Specifications and compatibility of the proposed container closure with the solution and leachables/extractables evaluation in consultation with the Toxicology division.
7. Proposed expiration dating of 24 months, and in-use shelf-life of [REDACTED] (b) (4).
8. Justification of the storage conditions for the primary stability batches and post approval implementation of ICH conditions as in the capsules (M1).
9. The applicant stated that biowaiver for the oral solution was granted in 2000 (M1). This should be verified in consultation with the ONDQA Biopharmaceutics group.

D. Comments for 74-day Letter:

1. Provide a summary of the current drug substance specifications to the current NDA.
2. Provide an extractables/leachables evaluation of the container/closure system with the oral solution and comparative data to support the proposed [REDACTED] (b) (4) [REDACTED] in your commercial closures.

E. **Recommendation for fileability:** The NDA is fileable based on pre-NDA agreements, sufficient number of primary stability batches, and 12 month real time stability data at 30°C/35% RH. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is not recommended for team review. The drug substance is not an NME, the formulation does not include novel excipients and the manufacturing process for the drug product does not present complexity, e.g., novel delivery or device issues, nor significant development. In addition, the primary stability batches are representative of the commercial batches.

Consults:

Since the preservative system is a well known conventional system a microbiology consult was not deemed necessary.

Specifications for impurities and leachables/extractables evaluation should be assessed in consultation with the Toxicology reviewer.
The biowaiver agreements cited and biowaiver request were consulted to the ONDQA Biopharmaceutics group.

Danae D Christodoulou, Ph.D.
Pharmaceutical Assessment Lead

4/3/2009
Date

Ali Al-Hakim, Ph.D.
Branch II Chief, ONDQA

04/06/2009
Date

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Categorical exclusion requested 21CFR 25.31(a)(d)
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Stability data have been provided with statistical analysis
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		All agreements of NDA 21-466 and related NDAs
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		Oral solution
16	Have all consults been identified and initiated?	√ N/A N/A N/A N/A N/A		Pharm/Tox Statistics OCP/CDRH/CBER LNC DMETS/ODS Microbiology

Have all DMF References been identified? Yes (√) No ()

DMF Number	Holder	Description	LoA Included	Status
			(b) (4) Yes	pending
			Yes	pending
			Yes	pending
			Yes	pending
			Yes	pending
			Yes	pending

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

/s/

Danae Christodoulou
4/6/2009 03:31:00 PM
CHEMIST
Initial Quality Assessment

Ali Al-Hakim
4/6/2009 04:32:34 PM
CHEMIST

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 22488/000	Sponsor:	PFIZER
Org. Code:	170		
Priority:	3		RINGASKIDDY CO, CORK, IRELAND
Stamp Date:	04-MAR-2009	Brand Name:	LYRICA (PREGABALIN)
PDUFA Date:	04-JAN-2010	Estab. Name:	
Action Goal:		Generic Name:	PREGABALIN
District Goal:	05-NOV-2009	Product Number; Dosage Form; Ingredient; Strengths	

FDA Contacts:	D. WALKER	Project Manager	(HFD-170)	301-796-4029
	J. HILL	Review Chemist		301-796-1679
	D. CHRISTODOULOU	Team Leader		301-796-1342

Overall Recommendation:	ACCEPTABLE	on 06-APR-2009	by E. JOHNSON	(HFD-320)	301-796-3334
	ACCEPTABLE	on 16-MAR-2009	by M. STOCK	(HFD-320)	301-796-4753

Establishment: **CFN:** **FEI:** 3003901862

PFIZER ASIA PACIFIC PTE LTD.
31 TUAS SOUTH AVENUE 6
SINGAPORE, , SINGAPORE

DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
file:	(b) (4)	OAI Status:	NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 06-APR-2009
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9611880 **FEI:** 3003382089

PFIZER IRELAND PHARMACEUTICALS
LITTLE ISLAND
COUNTY CORK, , IRELAND

DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	(b) (4)	OAI Status:	NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 17-MAR-2009
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 22488/000
Receipt Date: 04-MAR-2009
Regulatory: 04-JAN-2010

Action Goal:
District Goal: 05-NOV-2009

Applicant: PFIZER
 RINGASKIDDY CO, CORK, IRELAND

Brand Name: LYRICA (PREGABALIN)
Estab. Name:
Generic Name: PREGABALIN

Priority: 3
Org. Code: 170

Product Number; Dosage Form; Ingredient; Strengths

Application Comment:

FDA Contacts:	D. WALKER	Project Manager	(HFD-170)	301-796-4029
	J. HILL	Review Chemist		301-796-1679
	D. CHRISTODOULOU	Team Leader		301-796-1342

Overall Recommendation:	ACCEPTABLE	on 06-APR-2009	by E. JOHNSON	(HFD-320)	301-796-3334
	ACCEPTABLE	on 16-MAR-2009	by M. STOCK	(HFD-320)	301-796-4753

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** PFIZER ASIA PACIFIC PTE LTD.
 31 TUAS SOUTH AVENUE 6
 SINGAPORE, SINGAPORE

FEI: 3003901862

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: THIS FACILITY PERFORMS MANUFACTURING, RELEASE AND STABILITY TESTING FOR THE DRUG SUBSTANCE. (on 16-MAR-2009 by D. CHRISTODOULOU () 301-796-1342)

Profile: (b) (4); **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-MAR-2009				CHRISTODOULO
SUBMITTED TO DO	17-MAR-2009	GMP Inspection			STOCKM
DO RECOMMENDATION	06-APR-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	06-APR-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** 9611880 **FEI:** 3003382089

PFIZER IRELAND PHARMACEUTICALS

LITTLE ISLAND
COUNTY CORK, IRELAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: THIS FACILITY PERFORMS MANUFACTURING, RELEASE AND STABILITY TESTING OF THE DRUG SUBSTANCE. (on 16-MAR-2009 by D. CHRISTODOULOU () 301-796-1342)

Profile: (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-MAR-2009				CHRISTODOULO
OC RECOMMENDATION	17-MAR-2009			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9611016 FEI: 3002807852
 PFIZER IRELAND PHARMACEUTICALS INC.
 RINGASKIDDY API PLANT
 RINGASKIDDY, COUNTY CORK, IRELAND

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: THIS FACILITY PERFORMS MANUFACTURING, RELEASE AND STABILITY TESTING OF THE DRUG SUBSTANCE. FEI 3003882524 IS LISTED IN THE APPLICATION. SECOND CONTACT NAME: NORMA TIMMONS, PH. 353-21-432-8524 (on 16-MAR-2009 by D. CHRISTODOULOU () 301-796-1342)

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-MAR-2009				CHRISTODOULO
OC RECOMMENDATION	17-MAR-2009			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 1810189 FEI: 1810189
 PHARMACIA AND UPJOHN COMPANY, DIV. OF PFIZER, INC.
 7000 PORTAGE RD
 KALAMAZOO, MI 490010102

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE STABILITY TESTER

Estab. Comment: THIS FACILITY PERFORMS MANUFACTURE, PACKAGING, RELEASE AND STABILITY TESTING FOR THE COMMERCIAL DRUG PRODUCT. (on 12-MAR-2009 by D. CHRISTODOULOU () 301-796-1342)

Profile: LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS, **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	12-MAR-2009				CHRISTODOULO
SUBMITTED TO DO	13-MAR-2009	10-Day Letter			KIEL
DO RECOMMENDATION INSPECTION DATED 2/2-18/09 IS VAI. FIRM IS ACCEPTABLE.	16-MAR-2009			ACCEPTABLE BASED ON FILE REVIEW	PDOMINGO
OC RECOMMENDATION	16-MAR-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22488	ORIG-1	PFIZER INC	LYRICA (PREGABALIN)

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

/s/

NIKOO N MANOCHEHRI-KALANTARI
01/11/2010