

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-488**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

Department of Health and Human Services  
Food and Drug Administration

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use**

Form Approved: OMB No. 0910-0513  
Expiration Date: 04/30/10  
See OMB Statement on Page 3.

NDA NUMBER

22-488

NAME OF APPLICANT / NDA HOLDER

Parke Davis, Div. of Pfizer Inc.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

LYRICA

ACTIVE INGREDIENT(S)

pregabalin

STRENGTH(S)

20mg/ml

DOSAGE FORM

Oral solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

5563175

b. Issue Date of Patent

10/8/1996

c. Expiration Date of Patent

10/8/2013

d. Name of Patent Owner  
Warner-Lambert Co. LLC  
c/o General Patent Counsel  
Pfizer Inc.

Address (of Patent Owner)

235 East 42nd Street

City/State

New York, NY

ZIP Code

10017

FAX Number (if available)

Telephone Number

(212) 733-2323

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

Telephone Number

FAX Number (if available)

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ?  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) 1 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Claim 1 is directed to a method of treating seizure disorders with pregabalin. The Indications and Usage section of the proposed labeling describes adjunctive therapy for adult patients with partial onset seizures, and so is covered by the claim.

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

*Bruce A. Pokras*

2/2/2009

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

|   |  |
|---|--|
| <input type="checkbox"/> NDA Applicant/Holder | <input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official |
| <input type="checkbox"/> Patent Owner         | <input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official                      |
| Name<br>Bruce A. Pokras                       |  |
| Address<br>150 East 42nd Street               | City/State<br>New York, NY   |
| ZIP Code<br>10017                             | Telephone Number<br>(212) 733-6422   |
| FAX Number (if available)<br>(646) 563-9571   | E-Mail Address (if available)<br>bruce.a.pokras@pfizer.com   |

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

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Oral solution

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**1. GENERAL**

a. United States Patent Number

6001876

b. Issue Date of Patent

12/14/1999

c. Expiration Date of Patent

12/30/2018

d. Name of Patent Owner  
Warner-Lambert Co. LLC  
c/o General Patent Counsel  
Pfizer Inc.

Address (of Patent Owner)

235 East 42nd Street

City/State

New York, NY

ZIP Code

10017

FAX Number (if available)

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(212) 733-2323

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Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ?  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s)(as listed in the patent) 1, 2, 3, 5, 13, 15 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)  
 Claims 1 and 2 encompass the treatment of pain using a compound selected from a genus of compounds that includes pregabalin. Claim 3 encompasses the treatment of pain using pregabalin. Claims 5, 13 and 15 encompass the treatment of neuropathic pain, postherpetic pain and idiopathic pain, respectively, using a compound selected from a genus of compounds that includes pregabalin. The Indications and Usage section of the proposed labeling describes neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia (an idiopathic pain) and so are covered by the claims.

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

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**1. GENERAL**

a. United States Patent Number

6197819

b. Issue Date of Patent

3/6/2001

c. Expiration Date of Patent

12/30/2018

d. Name of Patent Owner

Northwestern University

Attn: Dr. Indrani Mukharji

Director, Technology Transfer Dept.

Address (of Patent Owner)

1880 Oak Avenue, Suite 100

City/State

Evanston, Illinois

ZIP Code

60201-3135

FAX Number (if available)

(847) 491-3625

Telephone Number

(847) 491-2105

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

|   |   |  |
|---|---|--|
| 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No            |
| 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?   | <input type="checkbox"/> Yes            | <input checked="" type="checkbox"/> No |
| 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). | <input type="checkbox"/> Yes            | <input type="checkbox"/> No            |
| 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.   |   |  |
|   |   |  |
| 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ?  | <input type="checkbox"/> Yes            | <input checked="" type="checkbox"/> No |
| 2.6 Does the patent claim only an intermediate?   | <input type="checkbox"/> Yes            | <input checked="" type="checkbox"/> No |
| 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  | <input type="checkbox"/> Yes            | <input type="checkbox"/> No            |

**3. Drug Product (Composition/Formulation)**

|  |   |  |
|--|---|--|
| 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No            |
| 3.2 Does the patent claim only an intermediate?  | <input type="checkbox"/> Yes            | <input checked="" type="checkbox"/> No |
| 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) | <input type="checkbox"/> Yes            | <input type="checkbox"/> No            |

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

|   |  |  |
|---|--|--|
| 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? | <input type="checkbox"/> Yes   | <input checked="" type="checkbox"/> No |
| 4.2 Patent Claim Number(s) (as listed in the patent)  | Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? |  |
|   | <input type="checkbox"/> Yes   | <input type="checkbox"/> No            |
| 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.   | Use: (Submit indication or method of use information as identified specifically in the approved labeling.)   |  |
|   |  |  |

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For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

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**Date Signed**

*Bruce A. Pokras*

2/2/2009

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| <input type="checkbox"/> Patent Owner         | <input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official                      |
| Name<br>Bruce A. Pokras                       |  |
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Rockville, MD 20857

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## EXCLUSIVITY SUMMARY

NDA # 22488

SUPPL #

HFD # 170

Trade Name

Generic Name Lyrica Oral Solution

Applicant Name C.P. Pharmaceuticals International C.V. C/O Pfizer Inc

Approval Date, If Known: January 4, 2010

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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

YES  NO

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

This bioavailability study compares the Lyrica Capsule approved under NDA 21-446, to the Lyrica Oral Solution.

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

d) Did the applicant request exclusivity?

YES  NO

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

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

YES NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

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

YES  NO

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

NDA# 21723 Lyrica (pregabalin) Capsules  
NDA# 21724 Lyrica (pregabalin) Capsules  
NDA# 21446 Lyrica (pregabalin) Capsules

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

summary for that investigation.

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

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

YES  NO

If yes, explain:

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Name of person completing form: Diana Walker  
Title: Regulatory Project Manager  
Date: December 15, 2009

Name of Office/Division Director signing form: Rigoberto Roca, M.D.  
Title: Deputy Director, Division of Anesthesia, Analgesia, and Rheumatology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22488

ORIG-1

PFIZER CHEMICAL LYRICA (PREGABALIN)  
CORP

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

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/s/

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PARINDA JANI  
01/04/2010

RIGOBERTO A ROCA  
01/04/2010

NDA 22-488

LYRICA<sup>®</sup> (pregabalin) Oral Solution 20 mg/mL

DEBARMENT CERTIFICATION

[FD&C Act 306(k)(1)]

Pfizer hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



\_\_\_\_\_  
Signature of Company Representative

16 February 2007

Date

## ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION   |                               |   |
|---|-------------------------------|---|
| NDA # 22488<br>BLA #  | NDA Supplement #<br>BLA STN # | If NDA, Efficacy Supplement Type:   |
| Proprietary Name: Lyrica<br>Established/Proper Name: Pregabalin<br>Dosage Form: Oral Solution, 20 mg/mL   |                               | Applicant: C.P. Pharmaceuticals International C.V.<br>Agent for Applicant (if applicable): Pfizer, Inc.   |
| RPM: Diana Walker   |                               | Division: DAARP   |
| <p><b>NDAs:</b><br/>                     NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)<br/>                     Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> |                               | <p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b><br/>                     Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input type="checkbox"/> No changes      <input type="checkbox"/> Updated<br/>                     Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p> |
| ❖ User Fee Goal Date<br>Action Goal Date (if different)   |                               | January 4, 2010   |
| ❖ Actions   |                               |   |
| • Proposed action   |                               | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE<br><input type="checkbox"/> NA <input type="checkbox"/> CR   |
| • Previous actions ( <i>specify type and date for each action taken</i> )   |                               | <input checked="" type="checkbox"/> None  |
| ❖ Promotional Materials ( <i>accelerated approvals only</i> )<br>Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____                           |                               | <input type="checkbox"/> Received   |

The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

|   |   |
|---|---|
| ❖ Application Characteristics <sup>2</sup>  |   |
| Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority<br>Chemical classification (new NDAs only): 3: New Formulation<br><br><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch<br><input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch<br><input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC<br><br>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)<br><input type="checkbox"/> Restricted distribution (21 CFR 314.520)<br>Subpart I <input type="checkbox"/> Approval based on animal studies<br><br><input type="checkbox"/> Submitted in response to a PMR<br><input type="checkbox"/> Submitted in response to a PMC<br><br>Comments: _____ |   |
| ❖ Date reviewed by PeRC (required for approvals only)<br>If PeRC review not necessary, explain: _____   | October 14, 2009  |
| ❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)  | <input type="checkbox"/> Yes, date  |
| ❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)   | <input type="checkbox"/> Yes <input type="checkbox"/> No  |
| ❖ Public communications (approvals only)  |   |
| • Office of Executive Programs (OEP) liaison has been notified of action  | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| • Press Office notified of action (by OEP)  | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| • Indicate what types (if any) of information dissemination are anticipated   | <input checked="" type="checkbox"/> None<br><input type="checkbox"/> HHS Press Release<br><input type="checkbox"/> FDA Talk Paper<br><input type="checkbox"/> CDER Q&As<br><input type="checkbox"/> Other |

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new RMS-BLA Product Information Sheet for TBP must be completed.

|  |   |
|--|---|
| ❖ Exclusivity  |   |
| <ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes   |
| <ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>   | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If, yes, NDA/BLA # _____ and date exclusivity expires: _____                       |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>   | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date exclusivity expires: _____                                       |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>   | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date exclusivity expires: _____                                       |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>  | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date exclusivity expires: _____                                       |
| <ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>   | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date 10-year limitation expires: _____                     |
| ❖ Patent Information (NDAs only)   |   |
| <ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>  | <input checked="" type="checkbox"/> Verified<br><input type="checkbox"/> Not applicable because drug is an old antibiotic.                                |
| <ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>   | 21 CFR 314.50(i)(1)(i)(A)<br><input type="checkbox"/> Verified<br><br>21 CFR 314.50(i)(1)<br><input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>  | <input type="checkbox"/> No paragraph III certification<br>Date patent will expire _____  |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</li> </ul> | <input type="checkbox"/> N/A (no paragraph IV certification)<br><input type="checkbox"/> Verified   |

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

|   |  |
|---|--|
| <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | <p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p> |
|---|--|

**CONTENTS OF ACTION PACKAGE**

|  |                 |
|--|-----------------|
| ❖ Copy of this Action Package Checklist <sup>3</sup> | January 4, 2010 |
|--|-----------------|

**Officer/Employee List**

|   |  |
|---|--|
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> ) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees  | <input checked="" type="checkbox"/> Included |

**Action Letters**

|   |  |
|---|--|
| ❖ Copies of all action letters ( <i>including approval letter with final labeling</i> ) | Action(s) and date(s)<br>Approval: January 4, 2010 |
|---|--|

**Labeling**

|  |   |
|--|---|
| ❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )   |   |
| <ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>           | December 22, 2009   |
| <ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul> | NA  |
| <ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>   | NA  |
| <ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>                              | NA  |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )               | <input checked="" type="checkbox"/> Medication Guide<br><input type="checkbox"/> Patient Package Insert<br><input type="checkbox"/> Instructions for Use<br><input type="checkbox"/> None |
| <ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>           | December 17, 2009   |

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 8/26/09

|   |   |
|---|---|
| <ul style="list-style-type: none"> <li>Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>  | NA  |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>  | March 4, 2009   |
| <ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>   | NA  |
| ❖ Labels (full color carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )  |   |
| <ul style="list-style-type: none"> <li>Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>   | NA  |
| <ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>   | December 7, 2009  |
| ❖ Proprietary Name <ul style="list-style-type: none"> <li>Review(s) (<i>indicate date(s)</i>)</li> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> </ul>   | Approved December 30, 2004, for the Lyrica Capsule NDA  |
| ❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )  | <input checked="" type="checkbox"/> RPM April 15, 2009<br><input checked="" type="checkbox"/> DMEDP<br>December 8, 2009<br>December 2, 2009<br>November 24, 2009<br><input checked="" type="checkbox"/> DRISK November 10, 2009<br><input checked="" type="checkbox"/> DDMAC<br>November 5, 2009<br>November 10, 2009<br><input type="checkbox"/> CSS<br><input type="checkbox"/> Other reviews |
| <b>Administrative / Regulatory Documents</b>  |   |
| ❖ Administrative Reviews (e.g., RPM Filing Review <sup>4</sup> /Memo of Filing Meeting) ( <i>indicate date of each review</i> )   | April 10, 2009  |
| ❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )   | <input checked="" type="checkbox"/> Included  |
| ❖ Application Integrity Policy (AIP) Status and Related Documents<br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>  |   |
| <ul style="list-style-type: none"> <li>Applicant in on the AIP</li> </ul>   | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| <ul style="list-style-type: none"> <li>This application is on the AIP             <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul> | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No<br><br><input type="checkbox"/> Not an AP action  |
| ❖ Pediatric Page ( <i>approvals only, must be reviewed by PERC before finalized</i> )   | <input type="checkbox"/> Included   |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )   | <input checked="" type="checkbox"/> Verified, statement is acceptable   |
| ❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )  |   |
| ❖ Internal memoranda, telecons, etc.  |   |
| ❖ Minutes of Meetings   |   |
| <ul style="list-style-type: none"> <li>PeRC (<i>indicate date of mtg; approvals only</i>)</li> </ul>  | <input type="checkbox"/> Not applicable<br>October 14, 2009   |

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 8/26/09

|  |   |
|--|---|
| • Pre-Approval Safety Conference ( <i>indicate date of mtg; approvals only</i> )   | <input checked="" type="checkbox"/> Not applicable  |
| • Regulatory Briefing ( <i>indicate date of mtg</i> )  | <input checked="" type="checkbox"/> No mtg  |
| • Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )  | <input type="checkbox"/> No mtg June 7, 2000  |
| • EOP2 meeting ( <i>indicate date of mtg</i> )   | <input checked="" type="checkbox"/> No mtg  |
| • Other (e.g., EOP2a, CMC pilot programs)  |   |
| ❖ Advisory Committee Meeting(s)  | <input checked="" type="checkbox"/> No AC meeting   |
| • Date(s) of Meeting(s)  |   |
| • 48-hour alert or minutes, if available ( <i>do not include transcript</i> )  |   |
| <b>Decisional and Summary Memos</b>  |   |
| ❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )   | <input checked="" type="checkbox"/> None  |
| Division Director Summary Review ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None January 4, 2010   |
| Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None November 23, 2009   |
| PMR/PMC Development Templates ( <i>indicate total number</i> )   | <input checked="" type="checkbox"/> None  |
| <b>Clinical Information<sup>5</sup></b>  |   |
| ❖ Clinical Reviews   |   |
| • Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )  | None  |
| • Clinical review(s) ( <i>indicate date for each review</i> )  | December 17, 2009   |
| • Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )  | <input checked="" type="checkbox"/> None  |
| ❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )  |   |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, review/memo explaining why not   | No new clinical data submitted.   |
| ❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )   | <input checked="" type="checkbox"/> None  |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )   | <input type="checkbox"/> Not needed<br>CSS Review: December 15, 2009<br>Consult: Drug abuse-related events: September 3, 2009 |
| ❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo (<i>indicate date</i>)</li> <li>• Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul> | November 30, 2009<br>January 4, 2010<br><input type="checkbox"/> None<br>December 14, 2009                                    |
| ❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )  | <input checked="" type="checkbox"/> None requested  |
| <b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None  |   |
| ❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None   |
| Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None   |
| <b>Biostatistics</b> <input checked="" type="checkbox"/> None  |   |

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 8/26/09

|   |  |
|---|--|
| ❖ Statistical Division Director Review(s) (indicate date for each review)   | <input type="checkbox"/> None  |
| Statistical Team Leader Review(s) (indicate date for each review)   | <input type="checkbox"/> None  |
| Statistical Review(s) (indicate date for each review)   | <input type="checkbox"/> None  |
| <b>Clinical Pharmacology</b> <input type="checkbox"/> None  |  |
| ❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)   | <input checked="" type="checkbox"/> None   |
| Clinical Pharmacology Team Leader Review(s) (indicate date for each review)   | <input checked="" type="checkbox"/> None   |
| Clinical Pharmacology review(s) (indicate date for each review)   | <input type="checkbox"/> None<br>Final Review: November 5, 2009<br>Initial assessment: July 17, 2009                           |
| ❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)   | <input checked="" type="checkbox"/> None   |
| <b>Nonclinical</b> <input type="checkbox"/> None  |  |
| ❖ Pharmacology/Toxicology Discipline Reviews  |  |
| • ADP/T Review(s) (indicate date for each review)   | <input checked="" type="checkbox"/> None   |
| • Supervisory Review(s) (indicate date for each review)   | <input checked="" type="checkbox"/> None   |
| • Pharm/tox review(s), including referenced IND reviews (indicate date for each review)   | <input type="checkbox"/> None<br>Final Review: November 6, 2009  |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)  | <input checked="" type="checkbox"/> None   |
| ❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)  | <input checked="" type="checkbox"/> No carc  |
| ❖ ECAC/CAC report/memo of meeting   | <input checked="" type="checkbox"/> None<br>Included in P/T review, page   |
| ❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)   | <input checked="" type="checkbox"/> None requested   |
| <b>Product Quality</b> <input type="checkbox"/> None  |  |
| ❖ Product Quality Discipline Reviews  |  |
| • ONDQA/OBP Division Director Review(s) (indicate date for each review)   | <input checked="" type="checkbox"/> None   |
| • Branch Chief/Team Leader Review(s) (indicate date for each review)  | <input checked="" type="checkbox"/> None   |
| • Product quality review(s) (indicate date for each review)   | <input type="checkbox"/> None<br>Review #2: November 6, 2009<br>Review #1: August 4, 2009<br>Initial assessment: April 6, 2009 |
| • ONDQA Biopharmaceutics review (indicate date for each review)   |  |
| • BLAs only: Facility information review(s) (indicate dates)  | <input checked="" type="checkbox"/> None   |
| ❖ Microbiology Reviews  |  |
| • NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)  | <input type="checkbox"/> Not needed  |
| • BLAs: Sterility assurance, product quality microbiology (indicate date of each review)  |  |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)   | <input type="checkbox"/> None<br>Biopharmaceutics: August 4, 2009  |
| ❖ Environmental Assessment (check one) (original and supplemental applications)   |  |
| <input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population) | March 4, 2009  |

|  |  |
|--|--|
| <input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )   |  |
| <input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )   |  |
| ❖ Facilities Review/Inspection   |  |
| <ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)</li> </ul>  | Date completed: April 6, 2009<br><input checked="" type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation  |
| <ul style="list-style-type: none"> <li>• BLAs:               <ul style="list-style-type: none"> <li>○ TBP-EER</li> <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)</li> </ul> </li> </ul> | Date completed:<br><input type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation<br>Date completed:<br><input type="checkbox"/> Requested<br><input type="checkbox"/> Accepted <input type="checkbox"/> Hold |
| ❖ NDAs: Methods Validation   | <input type="checkbox"/> Completed<br><input type="checkbox"/> Requested<br><input type="checkbox"/> Not yet requested<br><input checked="" type="checkbox"/> Not needed   |

### Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22488

ORIG-1

PFIZER CHEMICAL  
CORP

LYRICA (PREGABALIN)

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/s/

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PARINDA JANI

01/04/2010

**Walker, Diana**

**From:** Walker, Diana  
**Sent:** Tuesday, December 01, 2009 10:58 AM  
**To:** 'Shah, Imran (New London)'  
**Subject:** FDA Request for Information/Safety Update/01Dec09  
**Importance:** High

Dear Imran,

I have received the following information request from the review team. Please submit this information to you NDA as soon as possible before December 8, 2009.

**NDA 22-488 does not contain any safety information because no safety data are available for the oral solution formulation. Since pregabalin is a BCS Class I drug, we believe that safety data from the capsule formulation are relevant to labeling for the solution. Submit updated safety data for the capsule to NDA 22-488 as soon as possible. This submission could consist of the safety section of the last Annual Report for NDA 21-446 and Periodic Safety Update Reports (PSURs) for reporting periods between the closing date of the Annual Report and the most recent PSUR (if appropriate).**

Please contact me if you need clarification on any of these points.

Regards,

Diana

Diana L. Walker, Ph.D.  
Regulatory Project Manager  
FDA/CDER/ODE II/DAARP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: Diana.Walker@fda.hhs.gov

12/7/2009

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22488

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ORIG-1

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PFIZER CHEMICAL  
CORP

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LYRICA (PREGABALIN)

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/s/

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DIANA L WALKER  
12/07/2009

**Walker, Diana**

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**From:** Walker, Diana  
**Sent:** Friday, November 27, 2009 10:49 AM  
**To:** 'Shah, Imran (New London)'  
**Subject:** NDA 22488 Carton and Container Information Request 27Nov09  
**Importance:** High

Dear Imran,

I have received the following comments from the Division of Medication Errors Prevention regarding the container for Lyrica oral Solution, NDA 22488. Please respond to the following comments and submit a revised draft container label to your NDA for review as soon as possible.

**A. General Comments**

This product includes a medication guide and can be dispensed as a unit-of-use or in multiple uses. Ensure the quantity is sufficient to provide each patient with a medication guide.

**B. Container Label (Oral Solution)**

1. Revise the concentration (20 mg per 1 mL) to read, "20 mg per mL". NOTE: Delete '1' prior to 'mL'.
2. Revise the statement, "Each 1 mL contains 20 mg of pregabalin", to read "Each mL contains 20 mg of pregabalin".
3. Revise the statement, "NOT FOR PARENTERAL USE" to read "FOR ORAL USE ONLY".

Revise the statement, "DOSAGE AND USE...information" to read "Usual Dosage: See package insert for dosage information."

5. Increase the prominence and relocate the statement "Use within 45 days of first opening the bottle" to the top of the side panel to ensure that the user is aware that once the bottle is opened the product must be used within 45 days.
6. To allow the user to keep track of the 45 day expiration, provide a space to write the date the bottle is first opened.

Please feel free to contact me for clarification if necessary.

Regards,

Diana

Diana L. Walker, Ph.D.  
Regulatory Project Manager  
FDA/CDER/ODE II/DAARP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: Diana.Walker@fda.hhs.gov

12/7/2009

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22488

ORIG-1

PFIZER CHEMICAL  
CORP

LYRICA (PREGABALIN)

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/s/

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DIANA L WALKER  
12/07/2009

**Walker, Diana**

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**From:** Shah, Imran (New London) [Imran.Shah@pfizer.com]  
**Sent:** Wednesday, November 04, 2009 5:40 PM  
**To:** Walker, Diana  
**Subject:** RE: NDA 22488 Lyrica Oral Solution: Request for Clarification 03Nov09

Dear Diana

I can confirm that the Lyrica Oral Solution, 20 mg/mL, bottle has a child-resistant closure. I will submit this response to NDA 22-488 via an official submission too.

Kind regards  
Imran

---

**From:** Walker, Diana [mailto:Diana.Walker@fda.hhs.gov]  
**Sent:** Tuesday, November 03, 2009 3:53 PM  
**To:** Shah, Imran (New London)  
**Subject:** NDA 22488 Lyrica Oral Solution: Request for Clarification 03Nov09

Dear Imran,

Can you please confirm or clarify whether the Lyrica Oral Solution bottle has a child-resistant closure?

Kind regards,

na

Diana L. Walker, Ph.D.  
Regulatory Project Manager  
FDA/CDER/ODE II/DAARP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: Diana.Walker@fda.hhs.gov

11/5/2009

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22488

ORIG-1

PFIZER CHEMICAL LYRICA (PREGABALIN)  
CORP

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/s/

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DIANA L WALKER

11/05/2009



NDA 22488

**DISCIPLINE REVIEW LETTER**

Pfizer, Inc.  
50 Pequot Ave  
New London, CT 06320  
MS: 6025-B4162

Attention: Dr. S.I. Shah  
Associate Director, Regulatory Strategy  
Worldwide Regulatory Affairs & Quality Assurance

Dear Mr. Shah:

Please refer to your new drug application (NDA) dated and received March 4, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for LYRICA® (pregabalin) Oral Solution 20 mg/mL.

Our review of the Chemistry, Manufacturing, and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Provide information with respect to the homogenous nature of the drug product solution and that a precipitation, settlement or crystallization do not form after filling or during storage period.
2. Provide information with respect to the key/critical process parameters of the manufacturing process, including any holding step that may be used during the production of the Lyrica drug product.
3. Provide supportive data for the holding time of the bulk drug product as described in section 3.2.P.2.3, page 2, second paragraph. Additionally, provide information regarding the acceptable hold time based on the stability test data.
4. Provide information regarding the status of manufacturing process validation.
5. Provide a summary of the validation report for analytical procedures for the non-compendial excipient artificial strawberry flavor #11545.
6. Provide certificates from the manufacturers of the containers and closures indicating that these items have been appropriately tested and found to be compliant with applicable CFR regulations.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, contact Diana Walker, Ph.D., Regulatory Project Manager, at (301) 796-4029.

Sincerely,

*(See appended electronic signature page)*

Ali Al-Hakim, Ph.D.  
Chief, Branch II, DMPMA I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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ALI H AL HAKIM  
08/10/2009

**Walker, Diana**

**From:** Walker, Diana  
**Sent:** Monday, June 08, 2009 3:43 PM  
**To:** 'Shah, Imran (New London)'  
**Subject:** RE:NDA 22-488 Pediatric Studies submission 08Jun09

Dear Imran,

After a brief initial review of your recent submission on May 22, 2009, requesting a full waiver for all age groups and indications, the clinical review team found that you will need to resubmit your Pediatric Plan. You are not eligible to request a full waiver on the basis of ongoing studies for your other product. At this time you need to request a deferral of pediatric studies and submit a pediatric plan to support the deferral. You can request partial waivers as well, but must provide rationale for your request. If the results of the studies that are in progress for Lyrica capsules reveal that the product has either no efficacy or is efficacious in specific pediatric populations/for specific indications, then you may request a waiver based on either or both reasons at that time.

After looking at your pediatric studies for Lyrica capsules, this is what I found:

**Pediatric Study Plans: Lyrica Capsules**

**NDA:** 21-446 (1)/21-723(2)  
**Indication:** (1) pain assoc. with diabetic peripheral neuropathy  
(2) post-herpetic neuralgia  
**Request:** (1) Full Waiver – too few children to study  
(2) Full Waiver – too few children to study

**NDA:** 21-724  
**Indication:** (1) partial onset seizures  
**Request:** Waiver: 0-1 month  
Deferred pediatric study under PREA for the treatment of partial onset seizures in pediatric patients' ages 1 month [44 weeks gestational age] to 16 years. PMC- Final Report Submission Due: May 31, 2010

**NDA:** 21-446  
**Indication:** fibromyalgia  
**Request:** Partial Waiver (0-12 years) – disease doesn't exist in children, too few to study  
Deferral (13-16) – adult studies ready for approval, PMC – Final Report Submission Due: 2012

You can basically submit an identical request for the Lyrica Oral Solution. For (1) pain assoc. with diabetic peripheral neuropathy and (2) post-herpetic neuralgia (all age groups), for epilepsy/seizures, age 0-1 month, and for fibromyalgia age 0-12 years, you will need to request a waiver, and submit your rationale. For epilepsy/seizures ages 1 month-16 years and for fibromyalgia ages 13-16 years, you will need to request a deferral and submit a detailed description of your pediatric plan.

Once you have completed your studies for Lyrica Capsules (in 2010 and 2012), you can at that time submit a request for waiver of studies to the Oral Solution NDA, based on whatever the outcome was for the Lyrica Capsules.

I hope this all makes sense. Please let me know if you have any questions, otherwise I will look forward to your re-submission of your Pediatric Plan.

Regards,

Diana

Diana L. Walker, Ph.D.  
Regulatory Project Manager  
FDA/CDER/ODE II/DAARP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713

7/2/2009

Email: Diana.Walker@fda.hhs.gov

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**From:** Shah, Imran (New London) [mailto:Imran.Shah@pfizer.com]  
**Sent:** Friday, May 22, 2009 3:58 PM  
**To:** Walker, Diana  
**Subject:** RE: Lyrica NDA 22-488 Filing Letter 30Apr09

Dear Diana

Response to the 30 April information requests for both CMC and pediatrics has been submitted to NDA 22-488. I've attached cover letter for your convenience.

Please feel free to contact me if you have any questions.

Kind regards  
Imran

---

**From:** Walker, Diana [mailto:Diana.Walker@fda.hhs.gov]  
**Sent:** Thursday, April 30, 2009 2:39 PM  
**To:** Shah, Imran (New London)  
**Subject:** Lyrica NDA 22-488 Filing Letter 30Apr09  
**Importance:** High

Dear Imran,

I am attaching the Filing Notification letter for NDA 22-488, Lyrica Oral Solution. Note that the letter contains information requests for both Chemistry, Manufacturing, and Controls (CMC) and Pediatric information that we would like to receive as soon as possible.

Please review this letter, which is also being sent via regular mail, and feel free to contact me with any questions or clarifications.

Regards,

Diana

Diana L. Walker, Ph.D.  
Regulatory Project Manager  
FDA/CDER/ODE II/DAARP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: Diana.Walker@fda.hhs.gov

7/2/2009

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/s/

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Diana Walker  
7/17/2009 11:26:20 AM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-488

Pfizer, Inc.  
50 Pequot Ave  
New London, CT 06320

Attention: Dr. S.I. Shah  
Associate Director, Regulatory Strategy  
Worldwide Regulatory Affairs & Quality Assurance

Dear Mr. Shah:

Please refer to your new drug application (NDA) dated and received March 4, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for LYRICA® (pregabalin) Oral Solution 20 mg/mL.

We also refer to your submission dated March 13, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 4, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 30, 2009.

During our filing review of your application, we have identified the following deficiencies. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.



NDA 22-488  
Page 3

505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Anesthesia, Analgesia and Rheumatology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, contact Diana Walker, Ph.D., Regulatory Project Manager, at (301) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Bob Rappaport  
4/30/2009 01:24:13 PM

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

| <b>Application Information</b>   |  |  |
|--|--|--|
| NDA # <b>22-488</b><br>BLA#  | NDA Supplement #:S-<br>BLA STN #   | Efficacy Supplement Type SE-   |
| Proprietary Name: <b>Lyrica</b><br>Established/Proper Name: <b>pregabalin</b><br>Dosage Form: <b>Oral Solution</b><br>Strengths: <b>20 mg/mL</b>   |  |  |
| Applicant: <b>CP Pharmaceuticals International C.V.</b><br>Agent for Applicant (if applicable): <b>Pfizer, Inc.</b>  |  |  |
| Date of Application: <b>March 4, 2009</b><br>Date of Receipt: <b>March 4, 2009</b><br>Date clock started after UN:   |  |  |
| PDUFA Goal Date:<br><b>January 4, 2010</b>   |  | Action Goal Date (if different):<br><b>December 4, 2009</b>  |
| Filing Date: <b>May 3, 2009</b><br>Date of Filing Meeting: <b>April 7, 2009</b>  |  |  |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) : <b>3</b>  |  |  |
| Proposed Indication(s): <b>Neuropathic Pain, Epilepsy and Management of Fibromyalgia</b>   |  |  |
| Type of Original NDA:<br>AND (if applicable)<br>Type of NDA Supplement:  |  | <input checked="" type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)<br><input type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)      |
| <i>Refer to Appendix A for further information.</i>  |  |  |
| Review Classification:<br><br><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i><br><br><i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>                                    |  | <input checked="" type="checkbox"/> Standard<br><input type="checkbox"/> Priority<br><br><input type="checkbox"/> Tropical disease Priority review voucher submitted |
| Resubmission after withdrawal? <input type="checkbox"/>  |  |  |
| Resubmission after refuse to file? <input type="checkbox"/>  |  |  |
| Part 3 Combination Product? <input type="checkbox"/>   | <input type="checkbox"/> Drug/Biologic<br><input type="checkbox"/> Drug/Device<br><input type="checkbox"/> Biologic/Device   |  |
| <input type="checkbox"/> Fast Track<br><input type="checkbox"/> Rolling Review<br><input type="checkbox"/> Orphan Designation<br><br><input type="checkbox"/> Rx-to-OTC switch, Full<br><input type="checkbox"/> Rx-to-OTC switch, Partial<br><input type="checkbox"/> Direct-to-OTC<br><br>Other: | <input type="checkbox"/> PMC response<br><input type="checkbox"/> PMR response:<br><input type="checkbox"/> FDAAA [505(o)]<br><input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]<br><input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)<br><input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) |  |

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| Collaborative Review Division ( <i>if OTC product</i> ): DNP (however not OTC product)   |  |
| List referenced IND Number(s): IND 49,393, IND 53,763, IND (b) (4), IND 66,902, IND 76,815, IND (b) (4), NDA 21-723, NDA 21-724, NDA (b) (4), NDA 21-446   |  |
| PDUFA and Action Goal dates correct in tracking system?<br><br><i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| Are the proprietary, established/proper, and applicant names correct in tracking system?<br><br><i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?<br><br><i>If not, ask the document room staff to make the appropriate entries.</i>  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <b>Application Integrity Policy</b>  |  |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a></i><br><br>If yes, explain:<br><br>If yes, has OC/DMPQ been notified of the submission?<br><br>Comments:                            | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <b>User Fees</b>   |  |
| Form 3397 (User Fee Cover Sheet) submitted   | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| User Fee Status<br><br>Comments: ID # PD3009065, paid half-fee, no clinical data   | <input checked="" type="checkbox"/> Paid<br><input type="checkbox"/> Exempt (orphan, government)<br><input type="checkbox"/> Waived (e.g., small business, public health)<br><input type="checkbox"/> Not required |
| <i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>   |  |
| <b>Exclusivity</b>   |  |
| Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i><br><br>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO  |

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| <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>  |   |
| <p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>   | <p><input type="checkbox"/> YES<br/># years requested:<br/><input checked="" type="checkbox"/> NO</p>   |
| <p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>  | <p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES<br/><input type="checkbox"/> NO</p>   |
| <p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>   |   |
| <p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p> | <p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES<br/><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES<br/><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES<br/><input type="checkbox"/> NO</p> |

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| <p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p>  |           |                  | <input type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <p><b>If yes, please list below:</b></p>  |           |                  |   |
| Application No.   | Drug Name | Exclusivity Code | Exclusivity Expiration  |
|   |           |                  |   |
|   |           |                  |   |
| <p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p> |           |                  |   |
| <p><b>Format and Content</b></p>  |           |                  |   |
| <p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments:</b></p>  |           |                  | <input type="checkbox"/> All paper (except for COL)<br><input checked="" type="checkbox"/> All electronic<br><input type="checkbox"/> Mixed (paper/electronic)<br><br><input checked="" type="checkbox"/> CTD<br><input type="checkbox"/> Non-CTD<br><input type="checkbox"/> Mixed (CTD/non-CTD) |
| <p><b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b></p>  |           |                  |   |
| <p><b>If electronic submission:</b><br/> <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments:</b></p>   |           |                  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b>If electronic submission, does it follow the eCTD guidance?</b><br/> (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p>  |           |                  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b>If not, explain (e.g., waiver granted):</b></p>   |           |                  |   |

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| <p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b> Sent as amendment 3/13/2009</p>   | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO<br><br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>   | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible<br/> <input checked="" type="checkbox"/> English (or translated into English)<br/> <input checked="" type="checkbox"/> pagination<br/> <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p> | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b> Lyrica capsules- Final Rule July 28, 2005, Schedule V of the CSA.</p>  | <input type="checkbox"/> Not Applicable<br><br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO<br><br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO |
| <p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>   | <input type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <b>Patent Information (NDAs/NDA efficacy supplements only)</b>  |   |
| <p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <b>Debarment Certification</b>  |   |
| <p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p>   | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |

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| <p><i>sign the certification.</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p> <p><b>Comments:</b></p>  |   |
| <p><b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b></p>  |   |
| <p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>  | <p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>   |
| <p><b>Financial Disclosure</b></p>   |   |
| <p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b> No Clinical studies needed to support this application.</p>  | <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>   |
| <p><b>Pediatrics</b></p>   |   |
| <p><b>PREA</b></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul> | <p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> |

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| <b>Comments:</b>  |  |
| <b>BPCA (NDAs/NDA efficacy supplements only):</b>   |  |
| Is this submission a complete response to a pediatric Written Request?  | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO   |
| <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i> |  |
| <b>Comments:</b>  |  |
| <b>Prescription Labeling</b>  |  |
| Check all types of labeling submitted.  | <input type="checkbox"/> Not applicable<br><input checked="" type="checkbox"/> Package Insert (PI)<br><input checked="" type="checkbox"/> Patient Package Insert (PPI)<br><input type="checkbox"/> Instructions for Use<br><input type="checkbox"/> MedGuide<br><input type="checkbox"/> Carton labels<br><input checked="" type="checkbox"/> Immediate container labels<br><input type="checkbox"/> Diluent<br><input type="checkbox"/> Other (specify) |
| <b>Comments:</b> MedGuide for Lyrica Capsules under review in DNP with OSE/DRISK.                               |  |
| Is electronic Content of Labeling submitted in SPL format?  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <i>If no, request in 74-day letter.</i>   |  |
| <b>Comments:</b>  |  |
| Package insert (PI) submitted in PLR format?  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <b>If no</b> , was a waiver or deferral requested before the application was received or in the submission?     | <input type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <b>If before</b> , what is the status of the request?   |  |
| <i>If no, request in 74-day letter.</i>   |  |
| <b>Comments:</b>  |  |
| All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?                     | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <b>Comments:</b> MedGuide for Lyrica Capsules under review in DNP with OSE/DRISK.                               |  |
| MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )                     | <input type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO  |
| <b>Comments:</b> Lyrica MedGuide already under review with OSE/DRISK.   |  |
| REMS consulted to OSE/DRISK?  | <input type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO  |
| <b>Comments:</b> Lyrica MedGuide already under review with OSE/DRISK.   |  |
| Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?                | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <b>Comments:</b>  |  |

| <b>OTC Labeling</b>   |   |
|---|---|
| <p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>   | <input checked="" type="checkbox"/> <b>Not Applicable</b><br><input type="checkbox"/> Outer carton label<br><input type="checkbox"/> Immediate container label<br><input type="checkbox"/> Blister card<br><input type="checkbox"/> Blister backing label<br><input type="checkbox"/> Consumer Information Leaflet (CIL)<br><input type="checkbox"/> Physician sample<br><input type="checkbox"/> Consumer sample<br><input type="checkbox"/> Other (specify) |
| <p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>  | <input type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>                | <input type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>                | <input type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>                                      | <input type="checkbox"/> YES<br><input type="checkbox"/> NO   |
| <b>Meeting Minutes/SPA Agreements</b>   |   |
| <p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> YES<br>Date(s):<br><input checked="" type="checkbox"/> NO  |
| <p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>                               | <input checked="" type="checkbox"/> YES<br>Date(s): June 7, 2000.<br><input type="checkbox"/> NO  |
| <p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p> | <input type="checkbox"/> YES<br>Date(s):<br><input checked="" type="checkbox"/> NO  |

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 7, 2009

NDA/BLA #: 22-488

PROPRIETARY/ESTABLISHED NAMES: LYRICA (pregabalin)

APPLICANT: CP Pharmaceuticals International C.V.

Agent for Applicant: Pfizer, Inc.

BACKGROUND:

LYRICA® (pregabalin) Oral Solution, which was developed for patients who have difficulty swallowing capsules, is a new dosage form of pregabalin and will have the same indications as LYRICA (pregabalin) Capsules, as approved in NDA 21-446 and the 21-723 and 21-724 efficacy supplements. This NDA submission contains no new clinical, nonclinical, statistical or clinical-pharmacology data, but contains only new chemistry data for review.

REVIEW TEAM:

| Discipline/Organization                            | Names               |  | Present at filing meeting? (Y or N) |
|--|---------------------|--|-------------------------------------|
| Regulatory Project Management                      | RPM:                | Diana Walker   | Y                                   |
|  | CPMS/TL:            | Parinda Jani   | N                                   |
| Cross-Discipline Team Leader (CDTL)                | Danae Christodoulou |  | Y                                   |
| Clinical   | Reviewer and TL     | Robert Shibuya, MD                                     | Y                                   |
| Social Scientist Review (for OTC products)         | Reviewer:           | N/A  |                                     |
|  | TL:                 | N/A  |                                     |
| Labeling Review (for OTC products)                 | Reviewer:           | N/A  |                                     |
|  | TL:                 | N/A  |                                     |
| OSE  | Reviewer:           | LaToya Toombs, DMEPA                                   | Y                                   |
|  | TLs:                | Mary Dempsey, DRISK<br>Carlos Mena-Grillasca,<br>DMEPA | Y<br>Y                              |
| Clinical Microbiology (for antimicrobial products) | Reviewer:           | N/A  |                                     |

|  |  |                                     |        |
|--|--|-------------------------------------|--------|
| Clinical Pharmacology  | Reviewer:  | Suresh Naraharisetti                | Y      |
|  | TL:  | Suresh Doddapaneni                  | N      |
| Biostatistics  | Reviewer and TL                                  | Dionne Price                        | Y      |
| Nonclinical<br>(Pharmacology/Toxicology)                             | Reviewer:  | Kathleen Young                      | Y      |
|  | TL:  | Adam Wasserman                      | N      |
| Statistics, carcinogenicity  | Reviewer:  | N/A                                 |        |
|  | TL:  | N/A                                 |        |
| Product Quality (CMC)  | Reviewer:  | John Hill                           | Y      |
|  | TLs:   | Danae Christodoulou<br>Ali Al Hakim | Y<br>Y |
| Facility ( <i>for BLAs/BLA supplements</i> )                         | Reviewer:  | N/A                                 |        |
|  | TL:  | N/A                                 |        |
| Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> ) | Reviewer:  | N/A                                 |        |
|  | TL:  | N/A                                 |        |
| Bioresearch Monitoring (DSI)   | Reviewer:  | N/A                                 |        |
|  | TL:  | N/A                                 |        |
| Other reviewers  | Alicja Lerner, CSS reviewer<br>Lori Love, CSS TL |                                     | Y<br>Y |

**OTHER ATTENDEES:**

Sharon Hertz, MD  
 Jacqueline Ware, RPM, DNP  
 Philip Sheridan, MD, DNP  
 Chris Wheeler, RPM, OSE

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| 505(b)(2) filing issues?                 | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO |
| If yes, list issues:                     |   |
| Per reviewers, are all parts in English? | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| If no, explain:                          |   |

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|--|--|
| <p><b>Electronic Submission comments</b></p> <p>List comments: None</p>  | <input type="checkbox"/> Not Applicable  |
| <p><b>CLINICAL</b></p> <p>Comments:</p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p>If no, explain: No new clinical studies/data in application.</p>  | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO   |
| <ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul> | <input type="checkbox"/> YES<br>Date if known:<br><input checked="" type="checkbox"/> NO<br><input type="checkbox"/> To be determined<br>Reason:   |
| <ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p>Comments:</p>   | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b>CLINICAL MICROBIOLOGY</b></p> <p>Comments:</p>   | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter |
| <p><b>CLINICAL PHARMACOLOGY</b></p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE   |

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| <p><b>Comments:</b></p> <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>  | <input type="checkbox"/> Review issues for 74-day letter<br><input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO  |
| <p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter  |
| <p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter  |
| <p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> Three information requests to be sent.</p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input checked="" type="checkbox"/> Review issues for 74-day letter   |
| <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b> reviewed by CMC reviewer</p> | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO |
| <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b> Submitted by CMC reviewer</p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO<br><input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO          |
| <ul style="list-style-type: none"> <li>Sterile product?</li> </ul> <p><b>If yes</b>, was Microbiology Team consulted for</p>  | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO   |

|  |  |
|--|--|
| validation of sterilization? (NDAs/NDA supplements only)   |  |
| <b>FACILITY (BLAs only)</b>  | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter   |
| <b>Comments:</b>   |  |
| <b>REGULATORY PROJECT MANAGEMENT</b>   |  |
| <b>Signatory Authority:</b> Sharon Hertz, MD   |  |
| <b>GRMP Timeline Milestones:</b><br>Mid-Cycle: August 4, 2009<br>Wrap-Up: October 29, 2009<br>Labeling and PMR comments to Sponsor: November 30, 2009<br>Target Goal date: December 4, 2009<br>PDUFA date: January 4, 2010 |  |
| <b>Comments:</b>   |  |
| <b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>   |  |
| <input type="checkbox"/>   | The application is unsuitable for filing. Explain why:   |
| <input checked="" type="checkbox"/>  | The application, on its face, appears to be suitable for filing.<br><br><input type="checkbox"/> No review issues have been identified for the 74-day letter.<br><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):<br><br><input checked="" type="checkbox"/> Standard Review<br><br><input type="checkbox"/> Priority Review |
| <b>ACTIONS ITEMS</b>   |  |
| <input type="checkbox"/>   | Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.  |
| <input type="checkbox"/>   | If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.   |
| <input type="checkbox"/>   | If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.   |
| <input type="checkbox"/>   | If BLA or priority review NDA, send 60-day letter.   |
| <input type="checkbox"/>   | Send review issues/no review issues by day 74  |

|                          |       |
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|                          |       |
| <input type="checkbox"/> | Other |

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this page is the manifestation of the electronic signature.**  
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/s/

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Diana Walker  
4/10/2009 11:19:25 AM  
CSO

Worldwide Regulatory Affairs  
Pfizer Inc.  
50 Pequot Avenue  
New London, CT 06320



## Global Research & Development

04 March 2009

Bruce I. Skolnick  
Acting District Director  
Food and Drug Administration  
Office of Regulatory Affairs  
New York District Office  
158-15 Liberty Avenue  
Jamaica, New York 11433

THIS DOCUMENT CONTAINS CONFIDENTIAL AND/OR TRADE SECRET INFORMATION THAT IS DISCLOSED ONLY IN CONNECTION WITH THE LICENSING AND/OR REGISTRATION OF PRODUCTS FOR PFIZER INC OR ITS AFFILIATED COMPANIES. THIS DOCUMENT SHOULD NOT BE DISCLOSED OR USED, IN WHOLE OR IN PART, FOR ANY OTHER PURPOSE WITHOUT THE PRIOR WRITTEN CONSENT OF PFIZER INC.

Dear Mr. Skolnick

**RE: New Drug Application #22-488 - LYRICA® (pregabalin) Oral Solution 20 mg/mL**

Pursuant to 21 CFR § 11.2(b)(2) and the Office of Regulatory Affairs Memorandum dated 24 September 2003, Pfizer hereby certifies that a New Drug Application (identified as NDA 22-488) in electronic common technical document (eCTD) format for LYRICA® (pregabalin) Oral Solution was submitted to the Center for Drug Evaluation and Research's Central Document Room on 04 March 2009.

This submission is intended to request approval for a new pregabalin dosage form, an oral solution (20 mg/mL), based on the biowaiver agreements from the 07 June 2000 meeting between US Food and Drug Administration (FDA) and the sponsor (The Meeting Minutes Summary can be found in Module 1.6.3). This submission covers quality aspects, and no new clinical pharmacology, efficacy, or safety data are presented.

If you have any questions regarding this submission, please contact me at (860) 732 9080 or by e-mail [imran.shah@pfizer.com](mailto:imran.shah@pfizer.com) or send a facsimile to (860) 686-7607.

Sincerely,

Imran Shah  
Associate Director, Regulatory Strategy  
Worldwide Regulatory Affairs & Quality Assurance

IS/tw

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-488

**NDA ACKNOWLEDGMENT**

C.P. Pharmaceuticals International C.V.  
c/o Pfizer Inc.  
235 East 42nd Street  
New York, NY 10017

Attention: Imran Shah  
Associate Director, Regulatory Strategy  
Worldwide Regulatory Affairs & Quality Assurance

Dear Mr. Shah:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: LYRICA® (pregabalin) Oral Solution 20 mg/mL

Date of Application: March 4, 2009

Date of Receipt: March 4, 2009

Our Reference Number: NDA 22-488

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 3, 2009, in accordance with 21 CFR 314.101(a).

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under*

42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: [http://internet-dev.fda.gov/cder/regulatory/FDAAA\\_certification.htm](http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm). Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia and Rheumatology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-4029.

Sincerely,

*(See appended electronic signature page)*

Diana L. Walker, Ph.D.  
Regulatory Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Diana Walker  
4/2/2009 12:18:57 PM

**Walker, Diana**

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**From:** Walker, Diana  
**Sent:** Wednesday, March 11, 2009 11:13 AM  
**To:** 'Imran.Shah@pfizer.com'  
**Subject:** NDA 22-488/Lyrice/CMC Information request/11Mar09  
**Importance:** High

Dear Dr. Shah,

I would like to introduce myself. I have been assigned to work as the Regulatory Project Manager on your new NDA 22-488, Lyrice Oral Solution. I hope you will feel free to contact me via email or telephone if you have any issues or questions throughout this application review period.

I have received the following information request from our Division of Chemistry, Manufacturing and Controls (CMC) review team. Please submit this information to your NDA as soon as possible, but **no later than Monday, March 16, 2009**. It is essential that we receive this information as soon as possible so that we can request a facility evaluation.

**Update your NDA 22-488 with current drug substance manufacturing facility and contact information.**

Please contact me via email or telephone if you have any issues or questions about this information request.

Regards,

Diana

Diana L. Walker, Ph.D.  
Regulatory Project Manager  
FDA/CDER/ODE II/DAARP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: Diana.Walker@fda.hhs.gov

---

**From:** Sullivan, Matthew  
**Sent:** Thursday, March 05, 2009 2:56 PM  
**To:** Walker, Diana  
**Subject:** FW: Lyrice Oral Solution - NDA submission

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**From:** Shah, Imran (New London) [mailto:Imran.Shah@pfizer.com]  
**Sent:** Wednesday, March 04, 2009 4:15 PM  
**To:** Sullivan, Matthew  
**Cc:** Shah, Imran (New London)  
**Subject:** Lyrice Oral Solution - NDA submission

Hi Matt

NDA application 22-488, Lyrice Oral Solution, was filed to the FDA today. I've attached a copy of the cover letter to this email:

<<cover-letter-20090304-0000.pdf>>

3/12/2009

Lyrice Oral Solution - NDA submission

Page 2 of 2

Please let me know if you have any questions.

Kind regards

Imran

---

Dr S.I. Shah

Worldwide Regulatory Affairs - US

Pfizer Inc

50 Pequot Avenue

New London, CT 06320

(860) 732-9080 (phone)

(860) 686-7607 (fax)

3/12/2009

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this page is the manifestation of the electronic signature.**  
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/s/  
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Diana Walker  
3/12/2009 03:53:04 PM  
CSO

**Walker, Diana**

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**From:** Greeley, George  
**Sent:** Monday, December 14, 2009 9:58 PM  
**To:** Walker, Diana  
**Cc:** Stowe, Ginneh D.  
**Subject:** NDA 22-488 Lyrica

**Importance:** High

Hi Diana,

The Lyrica (pregabalin) full waivers and partial waivers, deferrals and plans were reviewed by the PeRC PREA Subcommittee on October 14, 2009.

The Division recommended a full waiver for the indications of **(1)** neuropathic pain associated with diabetic peripheral neuropathy (DPN) and **(2)** post herpetic neuralgia (PHN) because studies are impossible or highly impractical because there are too few children with disease/condition to study. The Division recommended a partial waiver because there are too few children with disease/condition and deferral because studies are underway for the oral formulation for the indications of **(3)** adjunctive therapy for patients with partial onset seizures (waiver 0-1 month, deferral 1 month - 16 years) and **(4)** fibromyalgia (waiver 0-12 years, deferral 13-16 years) because studies are ongoing with the oral formulation for this product.

The PeRC agreed with the Division to grant full waivers for the indications of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and post herpetic neuralgia (PHN).

The PeRC agreed with the Division to grant a partial waiver and deferral for the indications of adjunctive therapy for patients with partial onset seizures and fibromyalgia.

Thank you,

George Greeley  
Regulatory Health Project Manager  
Pediatric and Maternal Health Staff  
FDA/CDER/OND  
10903 New Hampshire Avenue  
Bldg. 22, Room 6467  
Silver Spring, MD 20993-0002  
Phone: 301.796.4025  
Email: [george.greeley@fda.hhs.gov](mailto:george.greeley@fda.hhs.gov)

 Please consider the environment before printing this e-mail.

**MEETING MINUTES**

**Meeting Date:** June 7, 2000      **Time:** 10:00 - 11:30      **Location:** WOC II  
**IND:** 49,393 and 53,763      **Meeting request date:** 3/17/00  
**Drug:** Pregabalin      **Date sponsor requested:** May/June 2000  
**Sponsor:** Parke-Davis Pharmaceutical Research      **Briefing document submission:** 5/5/00  
**Type of Meeting:** Pre-NDA Meeting

**Food and Drug Administration:**

|                          |  |
|--------------------------|--|
| Russ Katz, M.D.          | Division Director, DNDP                    |
| Karen Midthun, M.D.      | Division Director, DAAODP                  |
| Christina Fang, M.D.     | Medical Officer, DAAODP                    |
| Chang Lee, M.D.          | Medical Officer, DAAODP                    |
| Len Kapcala, M.D.        | Medical Officer, DNDP                      |
| Judy Racoosin, M.D.      | Medical Officer, DNDP                      |
| John Feeney, M.D.        | Neurology Team Leader, DNDP                |
| Armando Oliva, M.D.      | Medical Officer, DNDP                      |
| Philip Sheridan, M.D.    | Medical Officer, DNDP                      |
| Kun Jin, Ph.D.           | Biometrics Team Leader, HFD-710            |
| Kallapra Koti, Ph.D.     | Biometrics, HFD-710                        |
| Glenna Fitzgerald Ph.D.  | Pharmacology Supervisor, DNDP              |
| Stan Lin, Ph.D.          | Biometrics, HFD-725                        |
| Ray Baweja, Ph.D.        | Team Leader, PK, DNDP                      |
| Joga Gobburu, Ph.D.      | Biopharm, HFD-860                          |
| Vanitha Sekar, Ph.D.     | Biopharm, HFD-860                          |
| Jerry Fetterly, Ph.D.    | Biopharm, HFD-860                          |
| Dennis Bashaw, Ph.D.     | Team Leader, PK, DAAODP                    |
| Linda Carter             | ADRA, ODE I                                |
| Susan Wilson, DVM, Ph.D. | Pharmacology, DAAODP                       |
| Robert Osterberg, Ph.D.  | Acting Pharmacology Team Leader,<br>DAAODP |
| Sandra Cook              | Project Manager, DAAODP                    |
| Jackie Ware, Pharm.D.    | Project Manager, DNDP                      |
| Ed Fisher, Ph.D.         | Pharmacology, DNDP                         |

**Parke-Davis:**

Mark Pierce, MD, PhD      Clinical Research

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|                              |  |
|------------------------------|--|
| Betsy Garofalo, MD           | Clinical Research                        |
| Lloyd Knapp, PharmD          | Clinical Research                        |
| Mitch Brigell, Ph.D.         | Clinical Research                        |
| Ed Posvar, M.D.              | Clinical Pharmacology                    |
| Linda LaMoreaux, MPH         | Biometrics                               |
| Noel Mohberg, Ph.D.          | Biometrics                               |
| Howard Bockbrader, PhD       | Pharmacokinetics, Dynamics, & Metabolism |
| Zbigniew Wojcinski, DVM,DVSc | Toxicology                               |
| Mi Dong                      | Drug Development                         |
| Jan Turner, RN               | Regulatory                               |
| Byron Scott, R.Ph.           | Regulatory                               |
| Robin Pitts, R.Ph.           | Regulatory                               |
| Pauline Kim                  | Scientific Information Engineering       |

**Meeting Objective:**

The objective is to discuss the structure, format, and presentation of data for the NDA, which is scheduled to be submitted December 2000.

**Regulatory Status:**

There are currently 3 active INDs for Pregabalin (CI-1008) capsules. The targeted date for the first pregabalin NDA submission is December 2000. This NDA will be for the following indications:

- management of neuropathic pain or management of pain associated with diabetic neuropathy; and
- adjunctive therapy for patients with partial seizures, (b) (4)

(b) (4)

**NDA Proposals and Issues for Discussion**

**Note:** Parke-Davis questions are identified by bold typeface. FDA responses are in italics.

**General**

1. Indication-Pain

**Is our clinical plan to support an indication for management of neuropathic pain or management of pain associated with diabetic neuropathy as outlined in Attachment 1B acceptable for filing?**

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The proposed plan is acceptable. The issue of how the indication for neuropathic pain would be labeled will be a topic for the advisory committee. In addition, we have the following comments:

Data Issues:

- Duration of treatment is short (< 12 weeks) in the three diabetic neuropathy studies. The durability of the study drug's effect is an important factor in the assessment of efficacy in clinical studies. The 8-week study should be submitted in addition to the 5- and 6-week studies.
- Total diabetic patient exposure (to the dose 600 mg/day) may not meet ICH requirements. FDA prefers the safety database to contain patients using the highest recommended dose or heavily weighted toward patients using the highest recommended dose.

Efficacy Analyses

- Requested Additional Analyses:
  - Longitudinal analysis or area-under-curve method of the pain scale
  - Analysis of allodynia (or other measures of change in skin sensitivity) for patients with the symptom.
  - Rescue medication uses, including amount, time, frequency and types.
  - Analyses of SF-36 health related quality of life and Profile of Mood States (POMS)
  - Subset analyses: pain scores after removing patients who reported somnolence and dizziness

**2. Indication-add-on epilepsy**

Is our clinical plan to support an indication for adjunctive therapy for patients with partial seizure: (b) (4) as outlined in Attachment 1C acceptable for filing?

*In general, the proposed plan appears acceptable. It is possible that pregabalin may be considered a second line treatment for epilepsy depending on the review outcome of preclinical data on hemangiosarcome. The firm should be aware that the status of the indication is very much undetermined at this time.*

**3. Submission of One NDA**

- Is our proposal to request a single review across Divisions acceptable?**  
*An inter-Divisional review is planned. Specific review assignments will be determined at the filing meeting.*
- Is our plan to submit one NDA acceptable, or will the Agency assign a second NDA number to one of the indications for administrative purposes?**  
*Submission of one NDA is acceptable; however, it will be administratively split with two separate NDA numbers.*
- If the Agency assigns a second NDA number to one of the indications, will all correspondence go to both NDAs?**

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Yes.

- d. If the Agency assigns a second NDA number to one of the indications, will the Agency withdraw the administrative NDA once the application is approved?  
*We can not answer at this time.*

**4. Financial Disclosure Questionnaires**

*We note that Linda Carter [email dated May 22, 2000] provided feedback on your financial disclosure plans.*

**5. Electronic Regulatory Submission**

**Is our ERS plan acceptable?**

*We note an email from Randy Levin on May 20, 2000, provided his comments regarding the ERS. In addition, we request the following:*

- Each patient/subject should have a single, unique patient identification number across all data sets (i.e., a patient who goes from a controlled trial into an extension should keep the original patient identification number assigned in the controlled portion). At a minimum, a column could be added to each dataset indicating the patient's previous identification number.*
- When creating patient identification numbers, use consistent formatting across all datasets.*
- Include complete labels and codes for the data definition files (see example in section IV.K.Item 1.3 of the Guidance for Industry: Providing Regulatory Submissions in Electronic Format). Supplying the PROC CONTENTS in place of the data definition file (define.pdf) is not adequate.*
- It would be very useful if you could provide the SAS programs and a list of variables with the submission. A define.pdf file should be provided for statistics as well.*

**ITEM 5, Nonclinical Pharmacology and Toxicology**

**At this time we do not have any issues to discuss; however, we would appreciate any comments that the Division may have regarding the content and format of Item 5.**

*Please provide animal line listings.*

*In addition, please note that we will be closely reviewing the data submitted on hemangiosarcomas and will evaluate the risk/benefit ratio. These findings could have significant impact on approvability of the application. The outcome of this review may have profound effects on the entire application*

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*Parke-Davis noted that the final preclinical study reports on hemangiosarcomas would be submitted to the INDs in the very near future.*

**ITEM 6, Human Pharmacokinetics and Bioavailability**

6.

- a. **Does the Division agree that, based on the draft Biopharmaceutical Classification System, pregabalin is a Class I compound (high solubility/high permeability)?**
- b. **Does the Division agree that at a given strength and series (family of compositionally proportional formulations), the quality control dissolution data adequately confirm bioequivalence across formulations?**
- c. **Does the Division agree that the pregabalin dissolution data demonstrate that all immediate release formulations used in clinical trials are rapidly dissolving (b) (4) dissolved in 30 min)?**
- d. **Does the Division agree that comparisons of dissolution profiles of representative formulations demonstrate bioequivalence of all clinical formulations? For example: the low and high strength (25- and 150-mg) formulations of Series A and the low and high strength (75- and 300-mg) formulations of Series C are bioequivalent to 100-mg Series B formulation?**

*Assuming that the draft BCS guidance does not change, we agree with these proposals, based on review of the supporting data that has been submitted with this package.*

7. **Is our population pharmacokinetic analysis plan acceptable?**

*The proposal as described in the meeting package appears acceptable; however, specific details have not been provided.*

*Parke-Davis stated that they are following the FDA population pharmacokinetic guidance.*

8. **Is our plan to evaluate special patient populations and potential drug-drug interactions acceptable?**

*Special patient populations:*

*Please provide a justification, within the NDA submission, for not conducting a hepatic impairment study.*

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*Drug-drug interactions:*

*For the epilepsy indication, the proposal is acceptable. For the neuropathic pain indication, commitments for additional work may be requested, possibly as a phase IV commitment.*

*Parke-Davis noted that drug interaction information on phenobarbital and primidone will come from the Phase 3 epilepsy clinical trial data.*

9. Does the Division have any comments on the content and format of the PK/PD analysis?
- a. Provide rationale for use of average concentration versus other measures of exposure.
  - b. Please provide a rationale for the use of mean of seven daily scores as a pharmacodynamic measure for the pain studies.
  - c. The model on page 296 does not have a placebo effect. Consider incorporating a placebo-effect in the pharmacodynamic modeling exercise.
  - d. In addition to using the R-ratio as the pharmacodynamic endpoint for the epilepsy pharmacodynamic modeling, please also use seizure frequency as a pharmacodynamic measure in the pharmacodynamic modeling exercise.
  - e. The ERS (page 333) should include model code and output listing for the first and last models.

**ITEM 8 AND ITEM 10: Clinical and Statistical**

10. Is our outline of the ISE for both indications acceptable?

*Please see question 1 for comments.*

11.

- a. In addition to providing summaries of safety data from the controlled studies supporting the neuropathic pain and epilepsy claims, we will also pool data from all controlled and uncontrolled studies across all 3 therapy areas (pain, epilepsy, and (b) (4)). Summaries of pooled data will include demographics, exposure to pregabalin, and the frequency of all and associated adverse events (by body system and by decreasing frequency).

In these summaries, is it acceptable that data from the controlled (b) (4) will be included with the data from all other clinical studies despite the short duration?

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*The safety data from the acute and chronic studies should be summarized and presented separately. The data for each indication (diabetic neuropathic pain, non-neuropathic pain, epilepsy, (b) (4)) should be summarized and presented separately, as well. Within each indication, controlled trials and extension trials should be summarized and presented separately, by indication, in addition to being pooled into one group.*

*Parke-Davis asked if the analgesic open-label studies could be pooled. FDA advised that it was acceptable to pool open-label NON-diabetic safety data. FDA also asked for the data to be separated out into single-dose and multiple-dose categories.*

*For labeling presentation of adverse events, FDA stated that they may or may not have a joint "laundry list" of events; however, for clinical trial adverse event data, two separate safety presentations should be made.*

- b. **Various investigator terms from our studies code to the preferred COSTART term "Thinking Abnormal". We plan to review those terms in order to determine whether they can be classified into several subgroupings defined by more descriptive clinical terms that might be more informative for use in data summarization and possibly labeling. Is our plan acceptable?**

*Your proposal is acceptable, assuming source documents (e.g. physician descriptions from CRFs) are reviewed when creating the descriptive clinical term. FDA requested that Parke-Davis also provide a dictionary of terms.*

- c. **Is our plan to summarize the data from our on-going open-label studies in our ISS and not provide separate research reports for these ongoing studies acceptable?**

*In addition to being summarized in the ISS, open label studies should be described in individual study reports. These study reports may be "abbreviated" in the sense that efficacy data may not be complete. However, all safety data up to the study cut-off date should be summarized and presented.*

- d. **Are the following age categories for data summarization acceptable:**

- **Neuropathic Pain age categories:  $\geq 18$  to  $< 65$ ;  $\geq 65$  to  $< 75$ ;  $\geq 75$ ;**
- **Adjunctive Therapy-Partial Seizures age categories:  $\geq 12$  to  $< 17$ ;  $\geq 17$  to  $< 65$ ;  $\geq 65$  to  $< 75$ ;  $\geq 75$ ?**

*The proposal is acceptable.*

*Neuropharm comments/questions on the ISS:*

*Where in the electronic submission will the narratives for deaths, withdrawals due to AEs, and serious AEs be located? This should be marked clearly in the index for the ISS or clinical study reports.*

*On p. 167, in Table 6 "Overview of AEs" for the clinical pharmacology studies, "associated" AEs are to be summarized. What is the definition of "associated"?*

*Parke-Davis stated that the definition of associated was based on the investigator's designation. FDA advised that "associated" events should NOT be the focus of the the ISS. Parke-Davis agreed that it was not; their focus would be on all adverse events.*

*On pp. 168-9, clinical laboratory results and ECG results will focus on clinically significant "drug-related" abnormalities; how was drug-relatedness determined? All clinically significant abnormalities should be described whether or not they are "drug-related".*

*On p. 184, in Table 14 "Listing of Deaths" there are columns for the day of pregabalin the AE began, and the day of pregabalin the patient died. If the patient discontinued from the study treatment after the AE began, how will the time off drug prior to death be indicated? Also, will all deaths be included in the table, or only those occurring within a certain number of days after the last dose of study drug (e.g., 30 or 60)?*

*Parke-Davis stated that all deaths will be included. FDA requested that information be included on patient follow-up, laboratory values, and when the death occurred, and a methodology section describing how follow up was accomplished should also be included.*

*The appendices describing adverse events leading to discontinuation and serious adverse events should be broken down by study indication (e.g. epilepsy, pain, and psychiatry).*

*In appendix 15 describing the abnormal and very abnormal high and low laboratory values, please also include the normal range.*

*How will the QT length be measured, by the central reader or by machine? Parke-Davis stated that QT length would be measured by hand. What method will be used to correct the QT length for heart rate? We will attach our recommended method for standardizing the QT length. FDA does not prefer to use Bizet's correction method.*

*In appendix 18, if a patient discontinues prematurely, is the last on-study laboratory value used for the termination value? How are patients handled who don't have baseline values?*

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*For studies that included BID and TID dosing regimens with the same total dose (e.g., epilepsy study 009), please compare the common AE profiles of those groups.*

*Anti-inflammatory comments on safety:*

- *Requested Additional Analyses:*
  - *Subset Analyses: The safety outcome analysis for diabetic neuropathic pain patients should include:*
    - *blood pressure control, including change of drug regimen and doses*
    - *change in creatinine clearance (if available)*
    - *change in urinary albumin excretion (if available),*
    - *doubling of serum creatinine and*
    - *Symptomatic cardiac events.*
  - *Summary Table: Analysis of treatment-limiting AE (separate out dropouts due to AEs for diabetic neuropathy)*
  - *Significant changes over time (i.e. clinical scoring system) of clinical neurological evaluation on nerve function*
  - *CRFs: should include deaths, withdrawals and serious AEs for diabetic neuropathic pain studies*

**12. An analysis plan for evaluation of our ophthalmologic safety data was previously submitted on March 1, 2000.**

*Comments were provided via fax on 6/5/00, from Dr. Wiley Chambers. In addition, FDA stated that based on our experience with other drugs that have visual field problems, most patients seem to be asymptomatic. Consequently, the firm should not take much reassurance that events were not reported.*

*Parke Davis and FDA agreed to plan a separate meeting to clarify the analysis plan for evaluation of ophthalmologic safety data.*

- a. **The analysis plan for descriptive ophthalmologic safety data specifies the methods for using 4 sources of data to evaluate the incidence of visual function abnormalities. Additionally, an analysis of the quantitative visual field data is provided in the plan. These analyses will be carried out on the patients who were evaluated in the controlled trials in epilepsy, analgesia and psychiatry. Is this plan acceptable?**
- b. **The analysis plan for descriptive safety data also specifies our proposal to analyze the visual function adverse events that occur during long-term uncontrolled open label exposure. We propose to examine these data using a hazard analysis that shows the rate of events as a function of length of exposure to pregabalin (i.e. number of events occurring within a time interval divided by the number of patients exposed for this interval excluding patients with previous**

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events). The interpretation of this analysis will be done with reference to historical or other appropriate controls as well as to data from compounds with known retinal toxicity. Is this approach to the long-term uncontrolled data acceptable?

**13. Does the Agency have any comments with regard to our statistical analysis plans?**

*FDA has the following comments:*

- *For epilepsy: You plan to construct confidence intervals for the differences using the raw data. It is not clear what the purpose is and how it is connected to the primary analysis. Details (along with published references) should be provided.*
- *For analgesia: Include an analysis of the mean of the last 7 days of treatment (a version of last observation carried forward) as well as a sensitivity analysis.*

**ITEM 11, Case Report Form Tabulations**

**14. Case report form tabulations will be provided for all controlled and uncontrolled studies, including clinical pharmacology studies, for all exposures at the time of submission. As described in our attached ERS plan, SAS transport files will be provided for the domain profiles. An example of the datasets and variables from our CRF tabulations is provided in Attachment 12.**

**a. Is this acceptable?**

*At this time it can not be determined if the datasets and variables from the case report tabulations are acceptable because many of the variable names were inadequately labeled and explained in the PROC CONTENTS print-out. All abbreviations need to be explained.*

*Also, please explain your statement on page 339 (section 2.10) "Treatment values will only be stored in the demographics dataset." What do you mean by "treatment values"? If this means the subject's randomization group, that variable must be included in all datasets.*

*Additionally, please try to keep the datasets under the maximum size recommended in the Guidance for Industry: Providing Regulatory Submissions in Electronic Format.*

*A few specific comments can be made:*

- *Any adverse event dataset should include the investigator's verbatim term for the AE, the preferred term for the AE, and the system organ class (SOC).*

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cc: IND 49,393  
IND 53,763  
HFD-120/Div. File  
HFD-550/Div File  
HFD-550/Midthun  
HFD-120/Katz  
HFD-120/Feeney  
HFD-120/Kapcala/Racoosin  
HFD-120/Oliva/Sheridan  
HFD-550/Fang/Lee  
HFD-120/Fitzgerald/Fisher  
HFD-550/Wilson/Osterberg  
HFD-120/Ware  
HFD-550/Cook  
HFD-550/Lvaccari  
HFD-710/Jin/Koti  
HFD-725/Lin  
HFD-860/Baweja/Gobbura  
HFD-860/Sekar/Fetterly  
HFD-880/Bashaw

**MEETING MINUTES**

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/s/

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Jackie Ware

1/19/01 12:16:24 PM

Sandra Cook, Project Manager in DAAODP, signed these official minutes on the original paper copy.

Russell Katz

1/23/01 07:53:07 AM

Dr. Karen Mithun, Director of DAAODP, signed the official minutes on the original paper copy on 8/31/00.

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

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Jackie Ware  
5/18/01 01:39:09 PM  
Signed for John S. Purvis

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## Environmental Assessment

### Lyrica Oral Solution®

NDA#

20 mg/ml Pregabalin, 16 fl. oz. bottle

This application is for a new oral solution formulation for use in the treatment of all currently approved indications. As this new formulation will replace usage in the current population who has difficulty taking capsules, there will be no increase in environmental exposure.

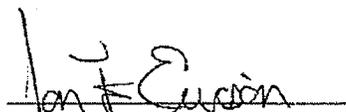
#### Claim for Categorical Exclusion According to 21 CFR Part 25.15 (a),(d)

Pfizer Inc claims a categorical exclusion to the environmental analysis requirements in accordance with categorical exclusion criteria 21 CFR Part 25.31 (a): Action on a NDA; if the action does not increase the use of the active moiety. Pfizer Inc claims that to the best of our knowledge no extraordinary circumstances exist.

#### Preparer:

Jon F. Ericson, Senior Principal Scientist, Pfizer Global Research and Development, Environmental Sciences, Pharmacokinetics, Dynamics and Metabolism, Groton, CT. Analytical Chemist with M.S. and 22 years experience in Drug Metabolism and Environmental Science.

The undersigned official states that the information presented is true, accurate, and complete to the best of Pfizer Inc's knowledge.

  
Jon F. Ericson

Senior Principal Scientist  
Environmental Sciences/ PDM  
Pfizer Global Research and Development  
Groton, CT 06340 USA

  
Date

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