

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021446Orig1s028**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**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*

NDA NUMBER  
21-446 (spinal cord injury supp)  
NAME OF APPLICANT / NDA HOLDER  
CP Pharmaceuticals Intl. CV, 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)  
25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg,  
300mg

DOSAGE FORM  
Capsule

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  
RE41920

b. Issue Date of Patent  
11/9/2010

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)

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

FAX Number (if available)

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

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

Yes  No

090177e1828f189AFinalFinal On: 22-Nov-1 09:56

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) 2, 5, 16, 17, 20, 21 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 2, 16 and 17 encompass the treatment of pain using pregabalin. Claims 5, 20 and 21 encompass the use of pregabalin for the treatment of the neuropathic pain. All of those claims encompass the management of neuropathic pain associated with spinal cord injury that is included in the Indications and Usage section of the proposed labeling for which approval is being sought in this supplement.

**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

090177e1828f189Final On: 22-Nov-1 09:56

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*

11/22/2011

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.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name  
Bruce A. Pokras

Address  
5 Giralda Farms

City/State  
Madison, NJ

ZIP Code  
07940

Telephone Number  
(973) 660-6583

FAX Number (if available)  
(646) 563-9571

E-Mail Address (if available)  
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:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, Room 400  
Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number*

090177e1828f189aFinal On: 22-Nov-11 09:56

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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  
3/6/2018

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)

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

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090177e1828f189AFinal\Final On: 22-Nov-11 09:56

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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

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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**

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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) 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.)

**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

090177e1828f189Final On: 22-Nov-1 09:56

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Date Signed

*Bruce A. Pokras*

11/22/2011

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Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name  
Bruce A. Pokras

Address  
5 Giralda Farms

City/State  
Madison, NJ

ZIP Code  
07940

Telephone Number  
(973) 660-6583

FAX Number (if available)  
(646) 563-9571

E-Mail Address (if available)  
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:

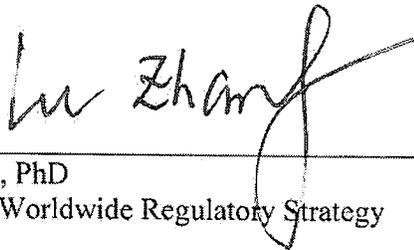
Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, Room 400  
Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number*

090177e1828f189\Final\Final On: 22-Nov- 1 09:56

**Debarment Certification**

Pfizer Inc. 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.



Lu Zhang, PhD  
Director, Worldwide Regulatory Strategy

Nov. 30. 2011

Date

090177e182955b6e\Final\Final On: 30-Nov-11 1 07:00

## EXCLUSIVITY SUMMARY

NDA # 021446

SUPPL # S-028

HFD # 170

Trade Name Lyrica

Generic Name pregabalin

Applicant Name PF PRISM CV, a Division of Pfizer, Inc.

Approval Date, If Known June 20, 2012

### 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

SE1

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.

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?

Three (3) years

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

YES  NO

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?

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# 21446 Lyrica  
NDA# 22488 Lyrica  
NDA# 21723 Lyrica  
NDA# 21724 Lyrica

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:

Investigation #1: Study A0081107: Central Neuropathic Pain Following Spinal Cord Injury

Investigation #2: Study 1008-000-125: Pregabalin for Treatment of Chronic Central Neuropathic Pain after Spinal Cord Injury  
Study 1008-000-125 was previously published in the literature, but was the Sponsor's study.

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

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1: Study A0081107: Central Neuropathic Pain Following Spinal Cord Injury

Investigation #2: Study 1008-000-125: Pregabalin for Treatment of Chronic Central Neuropathic Pain after Spinal Cord Injury

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
!  
IND # 53763 YES  ! NO   
Explain: !

CP Pharmaceuticals Intl. CV, a Division of Pfizer, is the sponsor named in the Form FDA-1571 for IND 53763 under which the new clinical investigations that are essential to approval of this supplemental NDA were conducted. The Sponsor has subsequently changed their name to PF PRISM CV, a Division of Pfizer, Inc. Although the name was changed, the Sponsor is the same.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

Investigation #2, 1008-000-125, was not carried out under an IND. Pfizer, Inc., submitted financial disclosure information on the following covered studies conducted under Pfizer SOPs: Studies A0081107 and 1008-000-125

(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:

=====  
Name of person completing form: Diana L. Walker, Ph.D.  
Title: Sr. Regulatory Health Project Manager  
Date: June 20, 2012

Name of Division Director signing form: Bob A. Rappaport, M.D.  
Title: Director, Division of Anesthesia, Analgesia, and Addiction Products  
Date: June 20, 2012

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

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

/s/  
-----

DIANA L WALKER  
06/20/2012

BOB A RAPPAPORT  
06/20/2012

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 021446 BLA #	NDA Supplement # S-028 BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Lyrica Established/Proper Name: pregabalin Dosage Form: capsules		Applicant: PF PRISM CV Agent for Applicant (if applicable): Pfizer, Inc.
RPM: Diana L. Walker, Ph.D.		Division: Anesthesia, Analgesia, and Addiction Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2) Efficacy Supplement:   <input checked="" 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 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(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"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   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>	
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>June 20, 2012</u></li> </ul>	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	<input checked="" type="checkbox"/> None	

<sup>1</sup> 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.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).



❖ 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)? <i>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.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes 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)? <i>(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.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes 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 <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) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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 Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <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>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	June 21, 2012
<b>Officer/Employee List</b>	
❖ 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
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s): Approval: June 20, 2012
<b>Labeling</b>	
❖ 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 draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	June 20, 2012
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	December 20, 2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Combined with Package Insert labeling, see above
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Combined with Package Insert labeling, see above
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	N/A N/A
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input type="checkbox"/> RPM <input type="checkbox"/> DMEPA <input checked="" type="checkbox"/> DMPP/PLT May 25, 2012 <input checked="" type="checkbox"/> ODPD May 17, 2012 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	RPM Filing Review: February 2, 2012
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<b>Application Integrity Policy (AIP) Status and Related Documents</b> <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 is 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  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>April 11, 2012</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ 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, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	included
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg September 30, 2011
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	May 20, 2005 July 28, 2006 September 27, 2006 May 4, 2007
❖ 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 June 20, 2012
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None June 7, 2012
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>6</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> )	Final: May 27, 2012 Filing: January 31, 2012
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Addressed in Clinical review dated May 27, 2012
❖ Clinical reviews from immunology and 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 checked="" type="checkbox"/> Not applicable

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management 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>	N/A N/A <input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested Review: May 16, 2012 Letter: April 20, 2012
<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 type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 25, 2012
<b>Clinical Pharmacology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input type="checkbox"/> None
<b>Nonclinical</b> <input checked="" type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input type="checkbox"/> None requested

<b>Product Quality</b>		<input type="checkbox"/> None
<b>❖ Product Quality Discipline Reviews</b>		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None June 18, 2012
<b>❖ Microbiology Reviews</b>		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
<b>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer</b> <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None
<b>❖ Environmental Assessment (check one) (original and supplemental applications)</b>		
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		
<input checked="" type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		May 16, 2012
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
<b>❖ Facilities Review/Inspection</b>		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<b>❖ NDAs: Methods Validation</b> <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix 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.

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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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DIANA L WALKER  
06/21/2012

**From:** [Walker, Diana](#)  
**To:** ["Zhang, Lu \(WRS\)"](#)  
**Subject:** Labeling revisions - sNDA 21446 S-028 31may12  
**Date:** Thursday, May 31, 2012 1:45:02 PM  
**Attachments:** [sNDA 21446 S-028 FDA Revisions - tracked - 31may12.doc](#)  
[sNDA 21446 S-028 FDA Revisions - tracked - 31may12.pdf](#)  
[sNDA 21446 S-028 FDA Revisions - clean- 31may12.pdf](#)

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Dear Lu,

Please find attached the FDA revisions to your proposed labeling for sNDA 21446 S-028. We accepted your proposed changes and then made revisions, which is what you will see reflected in the tracked changes. I am attaching a Word version of the tracked changes, and PDF versions of the tracked and clean label.

Please review the proposed FDA revisions, and email back to me your response. Please accept any changes with which you concur, and then make any revisions you deem necessary. Please DO NOT submit final labeling to the supplement NDA at this time, but send your response to me only via email. The reason is that we may have further labeling negotiations prior to the action date. We are still reviewing the label, so I want to stress that while these are fairly comprehensive, these may not be the final FDA revisions. Once we receive your response to these revisions, we will again review the label and then I will get back to you with any further proposed revisions prior to the action date.

Please let me know if you have any questions.

Kind regards,

Diana

Diana L. Walker, Ph.D.  
Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
05/31/2012

**From:** [Walker, Diana](#)  
**To:** ["Zhang, Lu \(WRS\)"](#)  
**Subject:** sNDA 21446 S-028 Lyrica Clinical Information Request 25may12  
**Date:** Friday, May 25, 2012 3:30:33 PM  
**Importance:** High

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Dear Lu,

I have received an information request for your NDA 21446 S-028 from our clinical review team. Please supply me with this information as soon as possible. You can submit this information to me first via email, followed by an official submission to your NDA Supplement.

**Please respond to the following:**

**In reference to your response (submitted May 23, 2012) to our information request (dated May 10, 2012 and clarified on May 15, 2012), the document titled "NP-SCI Other ADR List Document" lists neutropenia as a rare event under blood and lymphatic system disorders. In order to further characterize this event, provide case report form(s) and case narrative(s) with detailed laboratory information for the subjects in the NP-SCI population with neutropenia. Also provide the laboratory criteria used to define neutropenia.**

Please contact me if you need clarification on this request.  
Thank you for your assistance.

Kind Regards,  
Diana

Diana L. Walker, Ph.D.  
Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
05/29/2012

**From:** [Walker, Diana](#)  
**To:** ["Zhang, Lu \(WRS\)"](#)  
**Subject:** sNDA 21446 S-028 Lyrica Follow-up Clinical Information Request 21may12  
**Date:** Monday, May 21, 2012 4:14:32 PM  
**Importance:** High

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Dear Lu,

I have received an information request for your NDA 21446 S-028 from our clinical review team following up on your previous response to our information request dated May 10, 2012. Please supply me with this information as soon as possible, or no later than Wednesday, May 23, 2012. You can submit this information to me first via email, followed by an official submission to your NDA Supplement. Additionally, you can combine this response with your previous responses to our May 10, 2012 information request.

**Please respond to the following:**

**After reviewing your responses to our information request (dated May 10, 2012), we have determined that we need additional information. For the paragraph below, in Section 6.1 of the proposed labeling, confirm the numbers in red with and without the NP-SCI population (i.e., provide tables for this information in a similar format as Tables 1 and 2 in the "USPI Section 5 comparison document" contained in your recent email communication, dated May 18, 2012).**

***"Adverse Reactions Most Commonly Leading to Discontinuation in All Premarketing Controlled Clinical Studies***

**In premarketing controlled trials of all populations combined, 14% of patients treated with LYRICA and 7% of patients treated with placebo discontinued prematurely due to adverse reactions. In the LYRICA treatment group, the adverse reactions most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse reactions that led to discontinuation from controlled trials more frequently in the LYRICA group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema (1% each)."**

Please contact me if you need clarification on this request.

Thank you for your assistance.

Kind Regards,  
Diana

Diana L. Walker, Ph.D.  
Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029

Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
05/22/2012

**From:** [Walker, Diana](#)  
**To:** "[Zhang, Lu \(WRS\)](#)"  
**Subject:** sNDA 21446 S-028 Lyrica Clinical Information Request 10may12  
**Date:** Thursday, May 10, 2012 9:32:40 AM  
**Importance:** High

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Dear Lu,

I have received an information request for your NDA 21446 S-028 from our clinical review team. Please supply me with this information as soon as possible, or no later than Tuesday, May 15, 2012. You can submit this information to me first via email, followed by an official submission to your NDA Supplement.

**Please respond to the following:**

**Review of the proposed labeling reveals that several sections (i.e., Sections 5.5, 5.6, 5.7, 5.10, 5.11, 5.12, and 6.1) report numbers (i.e., adverse events and clinical laboratory parameters) that are common to all indications. As an example, in Section 5.6, the proposed labeling states that "In the LYRICA controlled trials, dizziness was experienced by 31% of LYRICA-treated patients compared to 9% of placebo-treated patients; somnolence was experienced by 22% of LYRICA-treated patients compared to 7% of placebo-treated patients."**

- **Verify that the numbers reported in these sections, as well as any other relevant sections in the label, are consistent when the central neuropathic pain-spinal cord injury population is included, and provide the source data used to derive these numbers.**

Please contact me if you need clarification on this request.  
Thank you for your assistance.

Kind Regards,  
Diana

Diana L. Walker, Ph.D.  
Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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DIANA L WALKER  
05/10/2012

**From:** [Greeley, George](#)  
**To:** [Walker, Diana](#)  
**Cc:** [Mathis, Lisa](#); [Addy, Rosemary](#); [Suggs, Courtney](#); [Lee, Catherine S.](#); [Rappaport, Bob A](#)  
**Subject:** NDA 21-446/028 Lyrica  
**Date:** Tuesday, April 17, 2012 1:44:10 PM  
**Attachments:** [1 Pediatric Record.pdf](#)  
**Importance:** High

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Hi Diana,

The email serves as confirmation of the review for Lyrica (pregabalin) conducted by the PeRC PREA Subcommittee on April 11, 2012.

The Division presented a full waiver in pediatric patients because studies are impossible or highly impracticable for the management of neuropathic pain associated with spinal cord injury because this condition does not occur in the pediatric population.

The PeRC agreed with the Division to grant a full waiver for this product.

The pediatric record is attached for Lyrica.

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.

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DIANA L WALKER  
04/17/2012

**From:** [Walker, Diana](#)  
**To:** ["Zhang, Lu \(WRS\)"](#)  
**Subject:** FW: sNDA 21446 S-028 Lyrica Clinical Information Request 13apr12  
**Date:** Friday, April 13, 2012 1:46:15 PM  
**Importance:** High

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Dear Lu,

I have received an information request for your NDA 21446 S-028 from our clinical review team. Please supply me with this information as soon as possible, or no later than Wednesday, April 18, 2012. You can submit this information to me first via email, followed by an official submission to your NDA Supplement.

**Please respond to the following:**

**To facilitate review of the materials you submitted in response to the Agency's information request dated April 4, 2012, provide Case Report Forms (CRFs) for the following subjects in Study A008-1107:**

**10121001  
10261005  
10491008  
10491012  
10491013  
10691005  
11021001  
11111006  
11161001  
11381002  
11481001  
11481007  
11491003  
11491005  
11531004  
11631005  
11701001  
11711002  
11761005**

Please contact me if you need clarification on this request.  
Thank you for your assistance.

Kind Regards,  
Diana

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

Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
04/17/2012

**From:** [Walker, Diana](#)  
**To:** "[Zhang, Lu \(WRS\)](#)"  
**Subject:** sNDA 21446 S-028 Lyrica Clinical Information Request 06apr12  
**Date:** Friday, April 06, 2012 1:40:31 PM  
**Importance:** High

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Dear Lu,

I have received an information request for your NDA 21446 S-028 from our clinical review team. Please supply me with this information as soon as possible, or no later than Thursday, April 12, 2012. You can submit this information to me first via email, followed by an official submission to your NDA Supplement.

**Please respond to the following:**

**The narrative you submitted for subject 11611002 (Study A008-1107), in response to item 4 of the filing communication (sent 2/13/12), is inadequate.**

**In Section 5.3.5.3.28, Table 5.1.6.a (Pregabalin Safety: CNP-SCI Submission, Listing of Permanent Discontinuations From Study, Appendix 1-9 safety tables and listings, p. 120) that subject is listed as discontinuing secondary to "other (it was assumed the clinical trial discontinuance from the result of Sheelian STS of Visit 4 by the investigator's judgment) [sic]." The narrative does not provide an explanation for the subject having been discontinued and does not address the statement made in the table, which requires clarification. Provide a narrative that clarifies the statement made in the table and clearly describes the reason for discontinuation.**

Please contact me if you need clarification on this request.  
Thank you for your assistance.

Kind Regards,  
Diana

Diana L. Walker, Ph.D.  
Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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DIANA L WALKER  
04/17/2012

**From:** [Walker, Diana](#)  
**To:** "[Zhang, Lu \(WRS\)](#)"  
**Subject:** sNDA 21446 S-028 Lyrica Clinical Information Request 04apr12  
**Date:** Wednesday, April 04, 2012 2:54:41 PM  
**Importance:** High

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Dear Lu,

I have received an information request for your NDA 21446 S-028 from our clinical review team. Please supply me with this information as soon as possible, or no later than Thursday, April 12, 2012. You can submit this information to me first via email, followed by an official submission to your NDA Supplement.

**Please respond to the following:**

**Interim application review and preliminary clinical site inspectional observations reveal that study sites recorded concomitant medications that were not in accordance with the protocol for Study A008-1107. Based on review of the protocol deviations for Study A008-1107 (Appendix B12), it is noted that these instances are not reported as protocol deviations.**

**1) Explain why concomitant medications that were prohibited by the protocol were not reported as protocol deviations.**

**2) Provide a table of all concomitant medication changes that occurred 30 days prior to Visit 1 and throughout the conduct of the study. For each concomitant medication change provide the following information:**

- **Subject identifier**
- **Date of Visit 1**
- **Date of study drug termination**
- **Date medication change occurred**
- **Study day medication change occurred**
- **Medication class**
- **Medication name**
- **Dose**
- **Dosing schedule**

Please contact me if you need clarification on this request.  
Thank you for your assistance.

Kind Regards,  
Diana

Diana L. Walker, Ph.D.  
Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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DIANA L WALKER  
04/17/2012

**From:** [Walker, Diana](#)  
**To:** "[Zhang, Lu \(WRS\)](#)"  
**Subject:** sNDA 21446 S-028 Lyrica Clinical Information Request 03apr12  
**Date:** Tuesday, April 03, 2012 12:05:24 PM  
**Importance:** High

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Dear Lu,

I have received an information request for your NDA 21446 S-028 from our clinical review team. Please supply me with this information as soon as possible, or no later than Wednesday, April 11, 2012. You can submit this information to me first via email, followed by an official submission to your NDA Supplement.

1. **We are unable to locate seven of the requested narratives (in item 3 of the filing communication sent February 3, 2012) in your responses dated March 9 and March 30, 2012. Please direct us to the location of the narratives listed below. If they were not provided, submit them.**

**Study A008-1107**

The following subjects are listed as experiencing SAEs in section 5.3.5.3.28, SD4 (Listing of Serious Adverse Events [All Causalities]-All Pregabalin Completed and Ongoing Studies, Appendix 1-9 - safety tables and listings, pp 803-4):

10551002  
10721012  
10791001  
11111007  
11761001  
11771002

**Study 1008-000-125**

The following subject is listed as discontinuing secondary to AEs in section 5.3.5.3.28, table 5.1.7.b (Pregabalin Safety: CNP-SCI Submission, Listing of Permanent Discontinuations Due to Adverse Events [All Causalities], Appendix 1-9 - safety tables and listings, p. 241):

4010

2. **Provide an explanation for the following discrepancies between narratives and patient data listings for study 1008-000-125:**
  - a. **Subject 6008: The narrative states this subject received placebo. However, in section 5.3.5.3.28, table 5.1.7.b (Pregabalin Safety: CNP-SCI Submission, Listing of Permanent Discontinuations Due to Adverse Events [All Causalities], Appendix 1-9 - safety tables and listings, p. 235) that same subject is listed as being part of the pregabalin group.**

**b. Subject 4020: The narrative indicates that the AE resulting in discontinuation occurred during the double blind treatment. However, in section 5.3.5.3.28, table 5.1.7.b (Pregabalin Safety: CNP-SCI Submission, Listing of Permanent Discontinuations Due to Adverse Events [All Causalities], Appendix 1-9 – safety tables and listings, p. 241) that subject is listed as discontinuing during open label treatment (under "Trt phase" "OL" is entered in parentheses for this subject).**

Please contact me if you need clarification on this request.  
Thank you for your assistance.

Kind Regards,  
Diana

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

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/s/  
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DIANA L WALKER  
04/17/2012

## Patwardhan, Swati

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**From:** Patwardhan, Swati  
**Sent:** Tuesday, March 13, 2012 4:26 PM  
**To:** 'lu.zhang@pfizer.com'  
**Subject:** NDA 21-446/S-028

Dear Dr. Zhang,

We are reviewing your Efficacy supplement for NDA 21-446/S-028 and request additional information as follows:

You have included two chronic studies in this application not previously submitted. You have also referenced the OECD guideline numbers for the studies used in the appendices (Appendix 8, OECD 210 AND Appendix 9, OECD 218), but the study reports and summaries are not included in the submission. Please submit the study reports and summaries for these two studies.

Please acknowledge the receipt. We request a response no later than Tuesday March 20, 2012. Please let me know if it not feasible at your end.

Thank you

Swati Patwardhan  
Regulatory Health Project Manager for Quality  
Office of New Drug Quality Assessment (ONDQA)  
Center of New Drug Evaluation and Research  
Phone: 301-796-4085  
Fax: 301-796-9748

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/s/  
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SWATI A PATWARDHAN  
03/13/2012



NDA 021446/S-028

**FILING COMMUNICATION**

P.F. PRISM C.V.  
c/o Pfizer, Inc.  
235 East 42<sup>nd</sup> Street  
New York, NY 10017

Attention: Lu Zhang, Ph.D.  
Director, Worldwide Regulatory Strategy

Dear Dr. Zhang:

Please refer to your Supplemental New Drug Application (sNDA) dated December 19, 2011, received December 20, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for LYRICA Capsules, 25, 50, 75, 100, 150, 200, 225 and 300 mg.

This supplemental application proposes the following new indication: neuropathic pain associated with spinal cord injury.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Priority**. Therefore, the user fee goal date is June 20, 2012.

We are reviewing your supplemental 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 requirement/commitment requests by May 30, 2012.

We request that you submit the following information:

1. In Section 5.3.5.3.28, we note in Table 3.3.b (Summary of Cumulative Exposure to Pregabalin by Daily Dose Range, Appendix 1-9 - safety tables and listings, p 100) that each subject could be counted in more than one row within a column. Provide an algorithm or rationale to calculate exposure totals (i.e., exposure data without duplicate representation of subjects within a column).
2. For Study 1008-000-02, provide a rationale for mandatory drug holidays and clarify how you derived chronic exposure data despite intermittent dosing.
3. Provide narratives (not MedWatch reports) for all Serious Adverse Events (SAEs) and all discontinuations secondary to Adverse Events (AEs).
4. Provide case report forms (CRFs) and narratives for the following subjects who discontinued secondary to “other” or “no longer willing to participate:”
  - a. A0081107: 1078-1001
  - b. A0081107: 1161-1002
  - c. A0081107: 1148-1002
  - d. 1008-000-125: 2-2012
  - e. 1008-000-125: 2-2013
  - f. 1008-000-125: 4-4001
  - g. 1008-000-125: 4-4037
  - h. 1008-000-125: 6-6014
  - i. 1008-000-125: 8-8006
  - j. A0081063: All 6 subjects in the study who discontinued secondary to “other” or “no longer willing to participate”
5. Provide CRFs and narratives for all deaths (if any occur), SAEs, and discontinuations secondary to AEs for ongoing Study A0081252.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit

consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Diana L. Walker, PhD, Regulatory Health Project Manager, at (301) 796-4029.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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BOB A RAPPAPORT  
02/03/2012

**From:** [Walker, Diana](#)  
**To:** ["Zhang, Lu \(WRS\)"](#)  
**Subject:** sNDA 21446 S-028 Lyrica Information Request 26jan12  
**Date:** Thursday, January 26, 2012 4:33:16 PM  
**Importance:** High

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Dear Lu,

Please verify the information for the following 4 clinical sites (Investigator names and addresses). Additionally, please supply us with contact information (telephone and email) for each of these investigators and sites. Please supply me with this information as soon as possible, or by Monday, January 30, 2012.

1. Center: 1100

Principal Investigator: Alina Agafina

St. Petersburg State Healthcare Institution City Hospital #  
40 Kurortnogo Administrativnogo Rajona  
Borisova ulitsa, 9, lit. B, Sestroretsk  
St.Petersburg  
197706  
RUSSIAN FEDERATION

2. Center: 1072

Principal Investigator: Dr. Michael Joseph Creamer

Rehabilitation Medical Group, P.A.  
100 West Gore Street  
Orlando  
FL  
32806  
UNITED STATES

3. Center: 004

Principal Investigator: Prof. Michael J. Cousins

Royal North Shore Hospital  
Department of Anaesthesia and Pain Management  
Pacific Highway  
St. Leonards, NSW 2065

4. Center: 006

Principal Investigator: Dr. Guy M. Bashford

Port Kembla Hospital  
(Illawarra)  
Cowper Street  
Warrawong, NSW 2502  
Australia

Thank you for your assistance.  
Kind Regards,  
Diana

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

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/s/  
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DIANA L WALKER  
01/31/2012



NDA 021446/S-028

**ACKNOWLEDGEMENT --  
PRIOR APPROVAL SUPPLEMENT**

C.P. Pharmaceuticals International C.V.  
c/o Pfizer, Inc.  
445 Eastern Point Road  
Groton, CT 06340

Attention: Lu Zhang, Ph.D.  
Director, Worldwide Regulatory Strategy

Dear Dr. Zhang:

We have received your Supplemental New Drug Application (sNDA), dated December 19, 2011, received December 20, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

**NDA NUMBER:** 021446  
**SUPPLEMENT NUMBER:** S-028  
**PRODUCT NAME:** LYRICA Capsules, 25, 50, 75, 100, 150, 200, 225 and 300 mg  
**DATE OF SUBMISSION:** December 19, 2011  
**DATE OF RECEIPT:** December 20, 2011

This supplemental application proposes the following new indication: neuropathic pain associated with spinal cord injury.

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 February 18, 2012, in accordance with 21 CFR 314.101(a).

**FDAAA TITLE VIII RESPONSIBILITIES**

You are also responsible for complying with the applicable provisions of sections 402(i) and (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).

## **SUBMISSION REQUIREMENTS**

Cite the application number listed above 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 Addiction 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, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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

Sincerely,

*{See appended electronic signature page}*

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

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DIANA L WALKER  
01/03/2012



IND 053763

**MEETING PRELIMINARY COMMENTS**

Pfizer Global Research and Development  
50 Pequot Ave.  
New London, CT 06320

Attention: Diane Shoda  
Lyrica Global Regulatory Lead,  
Worldwide Regulatory Affairs

Dear Ms. Shoda:

Please refer to your Investigational New Drug Application (IND) submitted July 24, 1997, received July 25, 1997, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lyrica (pregabalin) capsules.

We also refer to your July 8, 2011, correspondence, received July 8, 2011, requesting a meeting to discuss your proposed supplemental New Drug Application (sNDA) for Lyrica in the management of neuropathic pain associated with spinal cord injury.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 4, 2011, at 11 AM between you and the Division of Anesthesia, Analgesia, and Addiction Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

**PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

You should provide me a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1245.

Sincerely,

*{See appended electronic signature page}*

Matthew W. Sullivan, MS  
Senior Regulatory Project Manager  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE

**SPONSOR MEETING AGENDA**

**MEETING DATE:** October 4, 2011  
**TIME:** 11:00 am to 12:00 noon  
**LOCATION:** FDA White Oak Campus  
 Building 22, Room 1309  
**APPLICATION:** IND 053763  
**PRODUCT:** Lyrica (pregabalin)  
**PROPOSED INDICATION:** Management of neuropathic pain associated with spinal cord injury  
**SPONSOR:** Pfizer, Inc  
**TYPE OF MEETING:** Type B  
**MEETING CHAIR:** Frank Pucino, PharmD, MPH, Clinical Team Leader, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)  
**MEETING RECORDER:** Matthew Sullivan, MS, Senior Regulatory Project Manager, DAAAP

<b>FDA Attendees</b>	<b>Title</b>
Bob A. Rappaport, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Director, DAAAP
Frank Pucino, PharmD, MPH	Clinical Team Leader, DAAAP
Robert Levin, MD	Medical Officer, DAAAP
Ramesh Raghavachari, PhD	CMC Lead, Office of New Drug Quality Assessment (ONDQA)
Armaghan Emami, PhD	Pharmacology/ Toxicology Reviewer, DAAAP
Adam Wasserman, PhD	Pharmacology/ Toxicology Supervisor, DAAAP
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II (DCP II)
Yun Xu, PhD	Clinical Pharmacology Team Leader Division of Clinical Pharmacology II (DCP II)
Tom Permutt, PhD	Director, Division of Biometrics II (DBII)
Dionne Price, PhD	Statistical Team Leader, DBII
Jon Norton, PhD	Statistical Reviewer, DBII
Matthew Sullivan, MS	Regulatory Project Manager, DAAAP
<b>Pfizer Attendees</b>	<b>Title</b>
Henry Goebe, MD	Safety Risk Lead
Lloyd Knapp, PharmD	Executive Director, Clinical
Alex Kuperman	Director, Medical Doc & Labeling
Bruce Parsons, MD, PhD	Sr. Director, Medical Affairs
Luis Sanin, MD	Director, Clinical

Joseph Scavone, PharmD, MSc, MBA	Sr. Director, Clinical
Diane Shoda	Director, Worldwide Regulatory Strategy
Stephen Watt, MD	Sr. Director, Medical Affairs
Ed Whalen, PhD	Sr. Director, Statistics
Ruoyong Yang, PhD	Director, Statistics

## BACKGROUND

On July 8, 2011, the Sponsor submitted a meeting request to discuss their proposed supplemental New Drug Application (sNDA) for Lyrica in the management of neuropathic pain associated with spinal cord injury. The Division granted the meeting request, and agreed to discuss the questions during an October 4, 2011, meeting. The Sponsor subsequently submitted a background meeting package on August 11, 2011, in support of the meeting.

The questions from the August 11, 2011, meeting package are shown below in italics and Division responses are shown in normal text.

*Question 1: Does the Division agree that the efficacy studies that have been conducted are adequate and would support the review of the sNDA?*

### FDA Response:

The efficacy studies, as summarized in your briefing package, appear to be adequate to support the submission of an sNDA. However, final determination as to whether the studies are adequate to demonstrate efficacy cannot be made until the complete protocols, statistical analysis plans, and results are reviewed.

Based on the limited information that you have provided, we have the following comments about the proposed statistical analysis:

1. For Study 1107, the primary efficacy endpoint was the Duration Adjusted Average Change (DAAC). As we previously conveyed to you, a significant result on this endpoint would not support a finding of efficacy by itself. The primary endpoint must still be significant using a baseline observation carried forward (BOCF) analysis, or another analysis that assigns poor outcomes to patients who discontinue the study prematurely, particularly due to adverse events. While you state that the study showed significant results under an "mBOCF-MITT" analysis, this analysis was not clearly defined in the meeting package.
2. For Study 125, the primary efficacy analysis used last observation carried forward (LOCF) imputation. This is not an acceptable imputation method. You describe other approaches that you used or plan to use, but have not provided the results. The "mBOCF" analysis and "responder rates" have not been defined.

*Question 2: Given the study specific analyses for efficacy and the planned supplemental sensitivity analyses summarized in this briefing document, are there additional analyses that the Division would propose?*

FDA Response:

For each study, also submit a cumulative responder analysis, in which the proportions of subjects who have an improvement of >0%, >=10%, >=20%, etc., from baseline are shown graphically. Subjects who discontinue early for any reason should be assigned a value of 0. We may also request additional analyses in the course of the review.

*Question 3: Does the Division agree that the proposed efficacy data presentations, as detailed in the SCE TOC and list of summary tables, are appropriate to support the review of the sNDA?*

FDA Response:

Although, the overall presentation of the content for the Common Technical Document Module 2.7.3 Summary of Clinical Efficacy appears adequate, refer to our response to Question 4 regarding placement in the appropriate Modules.

*Question 4: Does the Division agree that all integrated efficacy data would be sufficiently detailed in the SCE such that providing the ISE would not be required?*

FDA Response:

No, we do not agree. Module 2 is intended for summary information. To facilitate the review of your NDA submission, we strongly recommend that the ISE and associated documents and data be placed in Module 5 in conformation with the Guidance for Industry Common Technical Document located at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

You are also directed to the following document that communicates general CDER preferences and experiences regarding the submission of standardized data to aid sponsors in the creation of standardized datasets:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM254113.pdf>

Additionally, the following link provides study specifications for submitting animal and human study datasets in electronic format:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>

*Question 5: Does the Division agree that the safety data, analyses, and planned presentations of the results, as detailed in the SCS TOC and list of summary tables/listings, are appropriate to support the review of the sNDA?*

FDA Response:

Although, the overall presentation of the content for the Common Technical Document Module 2.7.4 Summary of Clinical Safety appears adequate, refer to our response to Question 4 regarding placement in the appropriate Modules.

*Question 6: Does the Division agree that all integrated safety data would be sufficiently detailed in the SCS such that providing the ISS would not be required?*

FDA Response:

No, we do not agree. Refer to our response to Question 4.

*Question 7: Does the Division agree with the proposed safety narrative/patient profile plan?*

FDA Response:

Your proposed plan appears to be adequate; however upon review of the submitted data, additional information may be requested.

*Question 8: Does the Division agree with the proposed content of the 4-Month Safety Update?*

FDA Response:

The application must contain a sufficient number of patients in the safety database at the time of sNDA submission to assess the long-term safety for the intended patient population. Note that the additional safety data presented in the six-month interim report for ongoing Study 1252 may or may not be reviewed if submitted during the review cycle.

*Question 9: Does the Division agree with the outlined plan for pediatric development, including the waiver request?*

FDA Response:

We acknowledge that the small population of children with neuropathic pain associated with spinal cord injury make studies in this age range difficult. However, you will need to provide sufficient evidence that conducting these studies would be impossible or highly impractical, and therefore a statutory reason(s) for a waiver of pediatric studies has been met. The final decision to grant a pediatric waiver will need to be made by the Pediatric Review Committee (PeRC) during the review of your submission.

*Question 10: Does the Division agree with the proposal to cross-reference data on chemistry, manufacturing, and controls previously submitted to the Division in the original NDA?*

FDA Response:

There is no need to cross-reference the CMC data previously submitted. If there are any changes in the CMC information, it must be noted and supported in the submission.

*Question 11: Does the Division agree with the proposal to cross-reference nonclinical and clinical pharmacology data previously submitted to the Division in the original NDA?*

FDA Response:

There is no need to cross-reference nonclinical and clinical pharmacology data previously submitted. If there are any changes in the nonclinical or clinical pharmacology information, it must be noted and supported in the submission.

*Question 12: Does the Division agree with the proposed format and content of the electronic submission, as outlined in Appendix 12?*

FDA Response:

On face, it appears that the proposed format and content of the electronic submission are adequate.

*Question 13: Does the Division agree with the proposals outlined above regarding datasets and CRFs?*

FDA Response:

No, we do not agree. CRFs should be submitted for all SAEs, deaths and discontinuations due to adverse events, whether or not the clinical investigators attribute the event to be drug-related.

We recommend that you send SDTM-compliant tabulation files and analysis files. Further details can be found in the CDER Common Data Standards Issues Document:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM254113.pdf>.

We note that Study 125 was completed in 2004. If you submit CDISC data for this study, as we recommend, then we may also request the original data files if the need is identified in the course of review.

Other CDER data standards resources can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

*Question 14: Does the Division agree with Pfizer's proposal regarding financial disclosure?*

FDA Response:

Yes. We agree that you need to provide financial disclosure statements in the submission only for investigators involved in the conduct of the principal study used to establish the efficacy of your product.

*Question 15: Does the Division agree that this application could qualify for a priority review?*

FDA Response:

We would consider a priority review designation for a product that has the potential to provide safe and effective treatment for neuropathic pain associated with spinal cord injury.

A determination regarding whether a Priority or Standard Review will be assigned will be based on a preliminary review of the results of the studies submitted to support the proposed efficacy claim. We will inform you in writing of the review designation by Day 60 of the review.

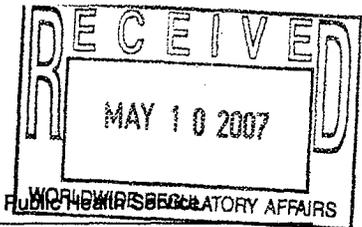
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MATTHEW W SULLIVAN  
09/30/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES



Food and Drug Administration  
Rockville, MD 20857

IND 53,763

MINUTES OF MEETING

Parke-Davis Pharmaceutical Research  
Attn: James Bammert, Pharm. D.  
Associate Director  
Worldwide Regulatory Strategy  
2800 Plymouth road  
Ann Arbor, MI 48105

Dear Dr. Bammert:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lyrica (pregabalin) Capsules C-V.

We also refer to the formal dispute resolution meeting between representatives of your firm and the FDA on March 15, 2007. The purpose of the meeting was to discuss the primary efficacy analysis for Protocol A0081107, a study of pregabalin in the treatment of chronic neuropathic pain associated with spinal cord injury.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1282.

Sincerely,

*{See appended electronic signature page}*

Leah W. Ripper  
Associate Director for Regulatory Affairs  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure  
Minutes of March 15, 2007, meeting

**MEMORANDUM OF MEETING MINUTES**

**Application Number:** IND 53,763  
**Product Name:** Lyrica (pregabalin) Capsules  
**Meeting Date:** Thursday, March 15, 2007  
**Meeting Time:** 3:00 – 4:30 p.m.  
**Meeting Location:** White Oak, Building 22, Room 1419  
**Meeting Type:** C  
**Meeting Category:** Response to Request for Formal Dispute Resolution  
**Received Briefing Package:** February 12, 2007  
**Sponsor Name:** Pfizer  
**Meeting Requestor:** James Bammert, Pharm.D. Associate Director,  
Pfizer  
**Meeting Chair:** Robert J. Meyer, M.D.  
**Meeting Recorder:** Lee Ripper

**Meeting Attendees:**

**FDA Attendees:**

Robert J. Meyer, M.D., Director, Office of Drug Evaluation II (ODE II), Office of  
New Drugs (OND)  
Lee Ripper, Associate Director for Regulatory Affairs, ODE II  
Bob Rappaport, M.D., Director, Division of Anesthesia, Analgesia, and  
Rheumatology Products (DAARP), ODE II  
Sharon Hertz, M.D., Deputy Director, DAARP  
Mwango Kashoki, M.D., M.P.H., Medical Team Leader (Analgesics), DAARP  
Ellen Fields, M.D. Acting Medical Team Leader (Analgesics), DAARP  
Jeffrey Siegel, M.D., Medical Team Leader (Rheumatology), DAARP  
Lisa Malandro, Regulatory Project Manager, DAARP  
Lauren Tornetta, M.S., Regulatory Project Manager, DAARP  
Robert O'Neill, Ph.D., Director, Office of Biostatistics (OB)  
Edward Nevius, Ph.D., Deputy Director (Acting), OB  
Thomas Permutt, Ph.D., Director (Acting), Division of Biometrics II (DB II), OB  
Dionne Price, Ph.D., Team Leader, DB II  
Joan Buenconsejo, Ph.D., Biostatistician, DB II  
Yongman Kim, Ph.D., Biostatistician, DB II  
Laurie Burke, R.Ph., M.P.H., Director, Study Endpoints and Label Development  
Team, OND  
Robert Temple, M.D., Director, Office of Medical Policy

**Sponsor Attendees:**

James Bammert, Pharm.D., Regulatory  
Mark Brown, M.D., Clinical  
Kevin Chartier, Ph.D., Biostatistics  
Teresa Griesing, Ph.D., Medical  
George Haig, Pharm.D., Clinical  
Lloyd Knapp, Pharm.D., Development  
Gary Koch, Ph. D., Consultant  
Jonathon Parker, R.Ph. M.S., Regulatory  
Kevin Phelan, Ph.D., Regulatory  
Ken Verburg, Ph.D., Development  
Christopher Wohlberg, M.D., Ph.D., Medical  
James Young, M.S. – Biostatistics

**1. BACKGROUND**

On November 1, 2006, Pfizer submitted to Dr. Robert Meyer a request for formal dispute resolution concerning the primary efficacy analysis requirements for Protocol A0081107, a study of pregabalin in the treatment of neuropathic pain associated with spinal cord injury. Prior to that request, Pfizer and DAARP had had several discussions regarding the primary efficacy analysis requirements without reaching a mutually acceptable conclusion. Pfizer's November 1 request proposed three possible remedies to the procedural and scientific disputes. Dr. Meyer accepted Pfizer's proposal to hold a meeting between Pfizer and FDA at which senior staff would engage in a scientific discussion on the merits and limitations of various methods of data analysis with the intent of determining methods that would be acceptable to both parties. The purpose of today's meeting is to engage in such a discussion.

**2. DISCUSSION**

2.1. After introductions, Mr. Parker gave Pfizer's introductory statement. Pfizer's position is that, for pain trials, FDA has historically accepted a last-observation carried forward (LOCF) imputation method for analysis of the primary endpoint for pain studies. DAARP had informed Pfizer that LOCF is no longer considered to be an acceptable imputation method for the primary analysis of pain studies and that baseline-observation carried forward (BOCF) or a similar approach, in which patients who discontinue due to adverse events are not assigned a favorable score, is the new standard. Pfizer stated that a landmark analysis does not take into account effects of treatment over the entire trial duration. Therefore, Pfizer proposed a duration-adjusted average change (DAAC) analysis for Protocol A0081107 which Pfizer believes will both evaluate efficacy over time, and appropriately handle missing data due to patient dropouts. However, the division indicated that DAAC would not be acceptable. Subsequently, Pfizer requested this meeting to allow both sides to fully exchange their viewpoints on the appropriate analyses for pain studies.

2.2. Dr. Hertz gave FDA's introductory statement (slides attached). FDA's reasons for requesting a BOCF analysis for pain studies are that

- The only benefit to patients from analgesic drugs is symptomatic treatment of pain.
- Pain relief is only present during the period of use of the product and does not persist following discontinuation of therapy.
- Chronic pain trials often have a substantial number of patients who drop out, mainly due to adverse events (AEs) and lack of efficacy.
- Some methods of imputation assign a good score to patients who experience a bad outcome; for example, use of LOCF for a patient who discontinues due to an AE.
- For a drug that confers no benefit other than symptomatic relief, efficacy results from patients who cannot tolerate the product are of questionable value for informing patient use.
- Therefore, conservative imputation methods that do not impute favorable scores for bad outcomes are preferred for the primary efficacy analysis. BOCF is only one such method; FDA does not require its use. Other approaches that appropriately address the concerns about drop-outs and missing data can also be considered.
- For a product intended to treat chronic pain, 12-week studies are intended to provide evidence of durable efficacy that can support use for months to years. Benefit demonstrated early in a study may not persist through to the end of the trial. It is necessary to demonstrate sustained improvement throughout the 12 weeks of treatment, including in the later time points. Therefore, FDA considers an analysis of efficacy at the end of the study (i.e., change from baseline to end of study, landmark analysis) as a more appropriate surrogate for long-term benefit than an analysis that averages results across the duration of the trial as the results could be driven by early data. DAAC does not provide a landmark analysis.
- FDA's concern with a DAAC analysis is that it attributes efficacy to patients who discontinue due to intolerable AEs, i.e., it assumes that even a brief period of improvement is beneficial. Such an analysis does not provide support for durability of effect.
- Any analysis using efficacy data from dropouts due to AEs would require confirmation that the finding of efficacy was not driven by data from dropouts (that is, the efficacy analysis must show that the patients remaining in the trial at the end were benefiting from treatment).

2.3 Points made and questions asked by Pfizer during the discussion:

- DAAC uses all observed pain data until patients drop out. DAAC evaluates efficacy over the entire time that patients are treated with drug.
- While less conservative than BOCF, DAAC is more conservative than LOCF.
- A drawback of the landmark analysis is that it will demonstrate efficacy in situations where patients only respond late in the course of treatment.
- Pfizer asked what is the deficiency in DAAC, other than that it does not provide a landmark analysis as the primary analysis? Pfizer also asked if the FDA would

object to the use of DAAC as the primary analysis if Pfizer would perform a landmark analysis with BOCF as a secondary assessment.

- Pfizer asked how the FDA would interpret efficacy if the DAAC result was favorable but the secondary landmark analysis failed.
- Pfizer asked whether, if DAAC was successful for all three doses but, due to AEs, efficacy was seen with the landmark analysis only at the two lower doses, the labeling could say something about efficacy at the higher dose, acknowledging poor tolerability. FDA deferred answering this question, stating that this is basically a review issue and would be discussed during labeling negotiations following complete analysis of the NDA.
- An alternative proposal would be to do an analysis using the average pain while on study drug, and the baseline values for the weeks after drop out. Pfizer contends this would be relevant in situations where patients might drop out due to AEs that are not so bad that patients would never take the drug again. This method would be more conservative than DAAC, but less conservative than BOCF. For patients who drop out very early, the imputation would be similar to BOCF.

#### 2.4 Points made by FDA during the discussion:

##### **Statistical Analysis**

- No particular method of analysis is required by FDA. However, the chosen method must be capable of showing that efficacy is not driven by patients who cannot tolerate the drug. A “win” cannot be driven by dropouts.
- Regardless of the imputation methodology that is employed to address the issue of missing data, FDA will evaluate the extent of dropouts due to lack of tolerance and weigh that in the risk/benefit analysis for products that provide only symptomatic (pain) relief. FDA will not approve analgesic products that reduce pain but cannot be tolerated and are therefore discontinued by patients.
- Demonstrating durability of effect is important for a chronic pain indication. FDA has seen instances of a lack of sustained efficacy in chronic pain trials. To complement a study that uses LOCF to impute missing data, or that uses a time weighted average analysis it would be necessary to provide a demonstration of durability of effect. One way to accomplish this would be to add a randomized withdrawal at the end of 12 weeks for all study completers.
- When the landmark analysis is positive, it is also informative to explore a time-weighted (AUC) analysis. In chronic pain trials, it is not uncommon to observe a pattern of dropouts in pain trials where patients discontinue at 5-6 weeks into the trial due to a lack of efficacy.
- One concern regarding the use of DAAC for the primary analysis and a landmark analysis as a secondary assessment is that if the trial ‘wins’ based on the DAAC but ‘fails’ on the landmark analysis, there will be no support for durability of effect. It would then be necessary to argue against a study that met its primary analysis.
- The efficacy analysis must address two issues: (1) the endpoint should be captured by the least biased analysis and (2) clinical utility must be shown.

### **Trial Design**

- FDA agrees that a fixed-dose study design can result in significant patient dropout. There are various study design methods for minimizing dropouts to lessen the concerns about conservative imputation strategies which could be used in certain settings. When a dosing range has already been determined, use of a titrate-to-effect design flexible dosing throughout the trial could be useful. It was noted that, given the stage of the study, substantial changes to the protocol would be difficult.
- Another option is flexible dosing throughout the trial, e.g. down titration of patients experiencing adverse events for products where dose-ranging information has otherwise been developed. In these instances, this design provides for a more “real-world” picture of use of the drug in clinical practice, and it minimizes dropouts.
- If prior data to establish dose-response are not available, a dose titration study still can be used to show persistent effect and a separate study can be used to show a dose-response effect.
- A randomized withdrawal design would show whether those completing the study on drug are actually experiencing efficacy. In this case, a landmark analysis would not be needed.

### **Additional comments:**

- While generally FDA would not approve an analgesic product where efficacy was seen solely in patients who could not tolerate the product, it could be possible to support approval for a product where there was a subgroup of patients who showed efficacy and tolerability, and this number was significant compared to placebo.

## **3. ACTION ITEMS**

- 3.1. Dr. Meyer agreed that, since new arguments had been made at today’s meeting, Pfizer could submit limited additional information and/or a new proposal and, depending on amount of material submitted and the review time available, he would try to take it into consideration.
- 3.2. Dr. Meyer will respond in writing to Pfizer’s Request for Formal Dispute Resolution within 30 days of this meeting.

## **4. POST-MEETING**

Pfizer submitted a proposal, dated March 29, 2007, received March 30, 2007, to use DAAC for the primary efficacy analysis in conjunction with use of mixed-models repeated measures (MMRM) techniques as a key secondary analysis.

**5. ATTACHMENTS AND HANDOUTS**

Dr. Hertz's slides, which were handed out at the meeting, are attached.

## FDRR Meeting

Sharon Hertz, M.D.  
Deputy Director  
Division of Anesthesia, Analgesia,  
and Rheumatology Products  
March 15, 2007

1

## Lyrica (pregabalin)

FDDR Discussion points:

- Strategies for handling missing data
- Landmark vs. Average Scores

2

## Chronic Pain Treatment

Analgesics provide symptomatic treatment of pain. There is no benefit to patients beyond symptom relief that, for most products, is only present during the period of use of the product, and does not persist following discontinuation of therapy.

3

## Missing Data in Chronic Pain Trials

Chronic pain trials often have a substantial number of patients who discontinue study participation early resulting in missing data.

Patient disposition in chronic pain trials is usually characterized by non-random, treatment-related dropouts :

- Active arm has more dropouts due to AEs
- Placebo arm has more dropouts due to lack of efficacy

4

## Missing Data in Chronic Pain Trials

Imputation methods for missing data are inherently imperfect.

- Some methods result in the imputation a good score for a bad outcome, e.g. LOCF for a patient that discontinues due to an adverse event.
- For a drug that is intended for symptomatic treatment that confers no other benefit, efficacy results from patients who cannot tolerate the product is of questionable value for informing efficacy in patients who can tolerate the product.

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## Missing Data in Chronic Pain Trials

- Therefore, conservative imputation methods that do not impute a good outcome are appropriate for the primary efficacy analysis
- Alternatively, analysis methods that do not require imputation can be used
  - Responder analysis that defines noncompleters as nonresponders regardless of reason for early discontinuation

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## Efficacy Analysis in Chronic Pain Trials

For a product intended to treat chronic pain, 12-week trials are intended to provide evidence of efficacy that can support use for months to years.

- Transient benefit early in the trial may not persist through to the end of the trial. It is necessary to demonstrate a sustained improvement at the 12-week timepoint.
- An analysis of efficacy based on the outcome at the end of the trial (landmark analysis) is a more appropriate surrogate for long-term benefit than an analysis that averages the results across the duration of the trial.

7

## Spinal Cord Injury Protocol

- R, DB, PC, fixed-dose, 4-arm trial
- Adults, non-progressive spinal cord injury with persistent central neuropathic pain
- 15 weeks duration, 12 weeks double-blind, fixed dose
- Treatment arms:
  - Lyrica (150, 300, and 600 mg/d)
  - Placebo

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## Spinal Cord Injury Protocol

- **Proposed primary endpoint:**
  - Average change in pain from baseline over the entire period of the study
    - Duration-adjusted average change (DAAC) to compute the endpoint
- **Secondary endpoints**
  - 30% and 50% responder rates

9

## Duration Adjusted Average Change (DAAC)

DAAC = mean of all daily pain scores minus the baseline score, multiplied by the proportion of the planned study duration that the patient completes

### Concerns:

- Attributes efficacy to patients who discontinue due to intolerable adverse events
  - Assumes that even a brief period of improvement is beneficial
- Does not provide support for durability of effect

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## Paths forward

- Landmark analysis with conservative imputation method
- Minimize dropouts through study design
  - Dosing based on titration to a tolerable dose, flexible-dose during randomized period
- Reduce noise
  - Evaluate efficacy over a wider timepoint, e.g. average pain over Weeks 11-12

11

## Paths forward

- Landmark analysis with less conservative imputation method (efficacy data from dropouts due to adverse events)
- Any analysis with efficacy data from dropouts due to AEs would require confirmation that finding of efficacy not driven by data from dropouts
  - e.g. randomized withdrawal period after the 12-weeks for study completers

12

## Paths forward

The division is open to discuss additional alternatives to address the problem of missing data and durability of effect.

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Leah Ripper  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 53,763

Parke-Davis Pharmaceutical Research, Division of Pfizer Inc.  
2800 Plymouth Road  
Ann Arbor, MI 48105

Attention: Jonathan Parker, RPh, MS  
Global Regulatory Leader, Worldwide Regulatory Strategy

Dear Mr. Parker:

Please refer to your Investigational New Drug Application (IND submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lyrica (pregabalin) Capsules.

We also refer to the teleconference between representatives of your firm and the FDA on August 28, 2006. The purpose of the meeting was to discuss the Division's official position on acceptable primary analysis methods for demonstrating efficacy.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1251.

Sincerely,

*{See appended electronic signature page}*

Lisa Malandro  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia,  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF TELECONFERENCE MINUTES

**MEETING DATE:** August 28, 2006  
**TIME:** 4:00 pm  
**APPLICATION:** IND 53,763  
**DRUG NAME:** Lyrica (pregabalin) Capsules

**MEETING RECORDER:** Lisa Malandro

### FDA ATTENDEES:

Bob A. Rappaport, M.D.  
Sharon Hertz, M.D.  
Thomas Permutt, Ph.D.  
Dionne Price, Ph.D.  
Lisa Malandro

### PFIZER ATTENDEES:

James Bammert, Pharm.D.  
Mark Brown, M.D.  
Cathryn Carter, M.S.  
Kevin Chartier, Ph.D.  
Lloyd Knapp, Pharm.D.  
Kevin Phelan, Ph.D.  
Molly Powers  
Ken Verburg, Ph.D.  
Christopher Wohlberg, M.D.  
James Young, M.S.

### BACKGROUND:

This teleconference was held in response to S-0459 dated August 18, 2006, which requested clarification of the Division's official position on acceptable primary analysis methods for demonstrating efficacy.

### DISCUSSION:

The Sponsor stated that there is a difference of opinion as to how missing data for <sup>(b) (4)</sup> spinal cord injury studies should be handled. The Sponsor requested an explanation of the Division's policy. The Sponsor's understanding of the Division's position is that the only primary analysis that will be considered by the Division is one which assigns a baseline (or worse) score to a patient who does not complete the study. Dr. Rappaport stated that the policy of the Division mandates use of a conservative imputation strategy such as one which assigns a baseline or worse score to patients who do not complete the study, and it has been discussed at IMMPACT, DIA, and other public venues. In addition, the policy has been vetted through senior management levels in the Agency. This policy will be formalized in the guidance document. Dr. Rappaport further stated that the Division is always open to new ideas and better

ways of doing things. The Division understands that achieving a good outcome can be difficult when using conservative imputation methods combined with commonly used study designs in pain trials.

Dr. Rappaport stated that there is a distinction between trials that treat symptomatic disorders and those that treat underlying disease states. Evaluations of analgesic studies are very different from other studies. If a patient cannot tolerate the side-effects of a pain medication, the medication has done them no good. This differs from an oncology drug where some benefit may be derived from any length of time a patient is able to tolerate the drug. For this reason, the Division believes a conservative approach to missing data is appropriate for analgesic trials. The Division also believes that responder analysis in which any early dropouts are considered nonresponders is an attractive approach for evaluation of analgesic trials as this approach results in no missing data.

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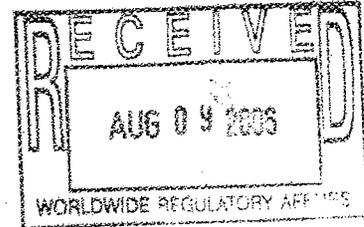
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 53,763

Pfizer Inc.  
2800 Plymouth Rd  
Ann Arbor, MI 48105

Attention: Jonathan Parker, R.Ph., M.S.  
Global Regulatory Leader



Dear Mr. Parker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lyrica® (pregabalin) Capsules C-V.

We also refer to the teleconference between representatives of your firm and the FDA on June 29, 2006. The purpose of the meeting was to discuss the Division's responses to your Special Protocol Assessment sent to you in a letter dated March 10, 2006.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1251.

Sincerely,

*{See appended electronic signature page}*

Lisa Malandro  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia,  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF TELECONFERENCE

DATE: June 29, 2006

APPLICATION NUMBER: IND 53,763

BETWEEN:

Representatives of Pfizer, Inc.

AND

Representatives of the Division of Anesthesia, Analgesia, and Rheumatology Products

SUBJECT: Type A meeting

The meeting package dated June 14, 2006 addressed the Division's recommendations outlined in a letter dated March 10, 2006. The letter was sent in response to Pfizer's request for a Special Protocol Assessment (SPA) of a Phase 3 study of Lyrica (pregabalin) as treatment for neuropathic pain associated with spinal cord injury (study A0081107).

During the teleconference held on June 29, 2006, Pfizer's responses to the SPA letter were discussed. The Division stated that the revisions to the protocol incorporating additional clinical assessments adequately addressed the Division's safety concerns. The Division also clarified that we are in agreement regarding the proposed continuous responder analysis.

The Division expressed continued disagreement with the proposed primary efficacy analysis. The Division explained that the desired primary efficacy analysis in chronic pain trials is a landmark analysis (i.e. an analysis evaluating drug effect at the end of treatment). The proposed duration adjusted average change (DAAC) in pain is not an appropriate strategy for a landmark analysis. The primary analysis must also utilize a reasonable imputation method that does not assign/impute "good" scores for patients who drop out due to "bad" outcomes (e.g. intolerable effects of the drug). Baseline-observation-carried-forward (BOCF) is an example of a methodology that appropriately assigns a "bad" outcome for drop-outs. A responder analysis (with dropouts counted as nonresponders) is an example of a landmark analysis that also does not ascribe a good score to individuals who discontinue the trial.

Assignment of a "bad" or negative score should also be made for patients who drop-out for reasons seemingly unrelated to safety or efficacy, such as "lost to follow-up," since such dropouts may in fact be treatment-related, and the drug is not effective in a patient who is no longer taking it. There is no basis for including a good score for a patient who did not complete the study.

For a chronic indication, the Sponsor must show that patients can take the drug at an appropriate dose and do well on it for the entire study. The Sponsor should choose an analysis method that does not rely on data for patients who cannot tolerate the drug. The patients included in the primary analysis must tolerate the drug for the entire trial duration. Patients who do not complete the study cannot have score included in the data that reflect efficacy.

IND 53,763  
Lyrica (pregabalin) Capsules  
Type A meeting  
June 29, 2006

The Division reiterated that BOCF imputation and responder analysis are just two suggestions of how the Sponsor can appropriately analyze the efficacy data. The Division remains open to other possible methods proposed by the Sponsor.

The Sponsor asked if there is a path forward for this drug that has tolerability issues in 70-80% of patients with spinal cord injury. The Division stated that they will assess the weight of evidence in the patient population. If the Sponsor demonstrates that the drug is effective in a subgroup of the patient population, it could be sufficient to support an application. All products have a range of responses and a range of responders. The Sponsor should use their Phase 2 trials to find appropriate methods to study a small population that might respond in order to learn how to demonstrate efficacy in the Phase 3 trials.

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Lisa Malandro  
Regulatory Health Project Manager

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DEPARTMENT OF HEALTH & HUMAN SERVICES

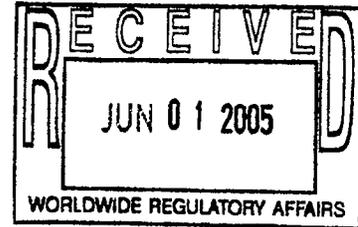
Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 53,763

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

Attention: Jonathan M. Parker, RPh, MS  
Global Regulatory Leader, Regulatory Affairs



Dear Mr. Parker:

Please refer to the meeting between representatives of your firm and FDA on April 21, 2005. The purpose of the meeting was to discuss the possibility of obtaining a general neuropathic pain claim for LYRICA (pregabalin) Capsules.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7416.

Sincerely,

*{See appended electronic signature page}*

Lisa Malandro  
Regulatory Health Project Manager  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

**Industry Meeting Minutes**

**Date/Time:** April 21, 2005/ 2:00 pm  
**Location:** Parklawn, Conference Room C  
**Application:** IND 53,763  
**Sponsor:** Pfizer, Inc.  
**Drug/Dosage Form/Doses:** Lyrica (pregabalin) Capsules  
**Indication:** General Neuropathic Pain  
**Type of Meeting:** Type C  
**Meeting Chair:** Rigoberto Roca M.D., Deputy Director  
**Minutes Recorder:** Lisa Malandro, Regulatory Project Manager

<b>Sponsor Attendees</b>	<b>Title</b>
James Bammert, R.Ph.	Regulatory
Elizabeth Garofalo, M.D.	Regulatory
Teresa Griesing, M.D.	Clinical
Rich Kavoussi, M.D.	Clinical
Lloyd Knapp, Pharm.D.	Development
Linda LaMoreaux, MPH.	Statistician
Paul Nitschmann, M.D.	Regulatory
Jonathon Parker, R.Ph., M.S.	Regulatory
Usha Rafferty, M.S.	Regulatory
Uma Sharma, Ph.D.	Clinical
Charles Taylor, Ph.D.	Pharmacology
Dave Wesche, M.D.	Clinical Pharmacology
<b>FDA Attendees</b>	<b>Title</b>
Bob A. Rappaport, M.D.	Division Director
Rigoberto Roca, M.D.	Deputy Director
Sharon Hertz, M.D.	Deputy Director, HFD-550
Celia Winchell, M.D.	Team Leader, Addiction Drugs
Tom Permutt, Ph.D.	Team Leader, Statistics
Mwango Kashoki, M.D., M.P.H.	Clinical Reviewer
Joan Buenconsejo, Ph.D.	Statistician
Lisa Malandro	Regulatory Project Manager

**BACKGROUND:**

In December, 2004, LYRICA (pregabalin) Capsules were approved for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and post-herpetic neuralgia (PHN). Pfizer, Inc. wishes to pursue development of pregabalin into a broader population of individuals and for the broad indication of "general neuropathic pain." This Type C meeting was held in order to discuss possible development paths forward.

**OPENING REMARKS:**

Dr. Rappaport opened the meeting by expressing the Division's interest in hearing Pfizer's rationale for a general neuropathic pain claim for LYRICA (pregabalin) Capsules, given the current debate among experts in neuropathic pain on the issue of a potential general claim. Dr. Uma Sharma of Pfizer, Inc. presented Pfizer's reasoning and proposal (see Attachment A).

**DISCUSSION:**

The Division stated that the FDA does not presently concur with the European Union's position on indications for neuropathic pain. The Division made the following comments in response to Pfizer's presentation:

1. A wide range of syndromes can be categorized as "neuropathic pain." These syndromes can vary greatly in terms of symptoms and pathophysiology. For example, DPN and phantom pain are due to different pathophysiological mechanisms. Also, cancer-related neuropathic pain can result from a wide spectrum of processes and symptoms can vary substantially, even within that one syndrome.
2. It is only partly true that neuropathic pain syndromes respond similarly to treatment. For example, while DPN and PHN have shown similar responses to therapy, pain associated with HIV neuropathy has failed to respond to that therapy. Therefore, there are sufficient differences in the various neuropathic conditions to raise questions as to whether efficacy in a few models of neuropathic pain would translate to all models.
3. An additional concern about provision of a general claim is the need to address a risk-benefit analysis for a drug across all types of neuropathic pain. Even if there was evidence of drug efficacy via a common mechanism and across multiple neuropathic pain conditions, there may not be the same balance of risk and benefit in these conditions. Any indication-specific safety issues including drug-drug interactions, drug-disease interactions, and interactions with other controlled substances must all be taken into consideration.
4. Without strongly supportive data, a broad neuropathic pain claim could misguide physicians and patients to use of the wrong treatment for the wrong indication. An inappropriately broad claim may promote a drug as being effective for a large group of conditions when, in fact, it may not be as effective as drugs that are currently used.
5. "Prevention of off-label use of drugs" is not a reason to establish a general neuropathic pain claim. The Agency does not regulate the practice of medicine. Off-label use of treatments can be valuable, particularly for refractory patients who often require trials of other therapies not specifically approved for their condition.
6. Development programs for general neuropathic pain indications would have to be very broad. Pfizer's current studies in neuropathic pain are not sufficiently broad enough for a general claim.

Although Pfizer's meeting package had asserted that the science on neuropathic pain has changed since the Advisory Committee held in 2002, the presentation did not include details on

new scientific information that would lead the Agency to reconsider decisions made at that meeting. Pfizer's staff described some additional pre-clinical studies, and presented data from one study, but was not able to provide detailed examples of new scientific data they felt supported a reconsideration of the Agency's approach. Dr. Rappaport stated that Pfizer should submit any new data that they have that supports their position with respect to a general claim to the Division for review. He added that all of the information that the Division has, including references from Pfizer's meeting package, show that drugs developed to treat neuropathies do not work across neuropathic pain indications.

Pfizer then inquired about feasibility of a general peripheral neuropathic pain claim. Dr. Hertz stated that this somewhat narrower indication could be considered if there was sufficient evidence that certain types of general neuropathic pain syndromes were similar in response to treatment. It was noted that the available information on pregabalin (comprising studies in DPN, PHN, and a population including both DPN and PHN) did not support broadening the indication to a general peripheral neuropathic claim, and that efficacy in other types of peripheral neuropathic pain would need to be demonstrated.

Dr. Rappaport added that to receive additional indication-specific peripheral pain claims for pregabalin, Pfizer need only provide one additional adequate and well-controlled trial for that indication. The Division would be willing to extrapolate safety and efficacy data from trials for approved indications to another trial in a different peripheral neuropathic pain population as appropriate.

With respect to obtaining a claim of efficacy of pregabalin in a specific central pain indication such as spinal cord injury, at least two adequate, well-controlled trials will be required. At this time, the scientific data do not support the provision of a general "central neuropathic pain" claim.

Dr. Rappaport concluded the meeting by stating that should Pfizer continue with its pursuit of a general neuropathic pain claim and submit the new scientific data that it believes support this indication, and the Division will take the matter back to the Advisory Committee for additional input.

**ACTION ITEMS:**

There were no action items.

Minutes prepared by:  
Lisa Malandro

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