

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-128

**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

22-128

NAME OF APPLICANT / NDA HOLDER

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)
CELSENTRI

ACTIVE INGREDIENT(S)
maraviroc

STRENGTH(S)
150mg; 300mg

DOSAGE FORM
Tablet

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
6586430

b. Issue Date of Patent
7/1/2003

c. Expiration Date of Patent
12/1/2019

d. Name of Patent Owner
Pfizer Inc.
General Patent Counsel

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

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

Yes No

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

2. Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2	Patent Claim Number (as listed in the patent) 19, 20	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
		<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Claim 19 encompasses the treatment of a disease that is ameliorated by CCR5 chemokine receptor antagonism by the administration of the drug for which approval is sought. Claim 20 encompasses the treatment or prevention of HIV infection by the administration of the drug for which approval is sought. Since HIV infection is a disease that can be ameliorated by CCR5 chemokine receptor antagonism, both of the recited claims encompass the treatment of CCR5-tropic HIV-1 infection found in the Indication and Usage section of the proposed 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

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

11/10/2004

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
201 Tabor Road

City/State
Morris Plains, NJ

ZIP Code
07950

Telephone Number
(973) 385-5399

FAX Number (if available)
(973) 385-7330

E-Mail Address (if available)
bruce.a.pokras@pfizer.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send

comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

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.

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1. GENERAL

a. United States Patent Number

6667314

b. Issue Date of Patent

12/23/2003

c. Expiration Date of Patent

5/25/2021

d. Name of Patent Owner

Pfizer Inc.
General Patent Counsel

Address (of Patent Owner)

235 East 42nd Street

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FAX Number (if available)

Telephone Number

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

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

City/State

ZIP Code

Telephone Number

FAX Number (if available)

E-Mail Address (if available)

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

Yes

No

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

Yes

No

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

2. Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 (as listed in the patent) 10 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Claim 10 encompasses a method of antagonizing a CCR5 receptor by the administration of the drug for which approval is sought. Since HIV infection is a disease that can be treated by antagonizing the CCR5 receptor in HIV-infected patients, the recited claim encompasses the treatment of CCR5-tropic HIV-1 infection found in the Indication and Usage section of the proposed 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

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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

11/18/2006

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Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Bruce A. Pokras	
Address 201 Tabor Road	City/State Morris Plains, NJ
ZIP Code 07950	Telephone Number (973) 385-5399
FAX Number (if available) (973) 385-7330	E-Mail Address (if available) bruce.a.pokras@pfizer.com

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

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EXCLUSIVITY SUMMARY

NDA # 22-128

SUPPL # n/a

HFD # 530

Trade Name SELZENTRY

Generic Name maraviroc

Applicant Name Pfizer Inc.

Approval Date, If Known August 6, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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?

5 years of marketing exclusivity following approval

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#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

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

YES NO

If yes, explain:

Name of person completing form: Kenny Shade
Title: Regulatory Health Project Manager
Date: August 6, 2007

Name of Office/Division Director signing form: Debra Birnkrant
Title: Division Director

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

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On Original**

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-128 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: December 20, 2006 PDUFA Goal Date: June 20, 2007

HFD 530 Trade and generic names/dosage form: SELZENTRY™ (maraviroc) 150 mg and 300 mg tablets

Applicant: Pfizer Inc. Therapeutic Class: Antiviral

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
- No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of HIV-1 infection

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): December 2011 and December 2015

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 22-128

Page 3

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

**Appears This Way
On Original**

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

Kenny Shade

8/6/2007 01:29:44 PM

NDA 22-128

CELSENTRI® (maraviroc) Oral

DEBARMENT CERTIFICATION

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

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

Seilani V. Kapili

Signature of Company Representative

05 December 2006

Date

PFIZER CONFIDENTIAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 6, 2007

FROM: Kenny Shade

SUBJECT: **Discussion of Postmarketing Commitments**
NDA 22-128, SELZENTRY (maraviroc) 150 mg and 300 mg tablets

On Friday August 3, 2007 Leilani V. Kapilli, Director, Worldwide Regulatory Affairs and Quality Assurance representing Pfizer Inc. Kenny Shade, RPM and Scott Proestel, MD from the Division of Antiviral Products, had a brief teleconference to discuss and finalize the postmarketing commitments for NDA 22-128 SELZENTRY™ (maraviroc). The following Postmarketing Commitments were finalized:

1. Submit Week 48 reports and datasets for Studies A4001027 and A4001028.

Week 48 report submission: August 2007

2. Deferred pediatric study under PREA for the treatment of HIV in pediatric subjects from 2 to 18 years of age. This study will determine the maraviroc exposure (pharmacokinetics profile) followed by 48 weeks of dosing, with efficacy based on viral load reduction through 48 weeks of dosing, and safety monitored over 96 weeks for pediatric subjects from 2 to 18 years of age to support maraviroc dose selection, safety and efficacy.

Protocol Submission Date: December 2007

Final Study Report Submission Date: December 2011

3. Deferred pediatric study under PREA for the treatment of HIV in pediatric subjects from birth to ≤ 2 years of age. This study will determine the maraviroc exposure (pharmacokinetic profile) followed by 48 weeks of dosing with efficacy based on viral load reduction through 48 weeks of dosing, and safety monitored over 96 weeks for pediatric subjects from birth to 2 years of age to support maraviroc dose selection, safety and efficacy.

Protocol Submission Date: December 2007

Final Study Report Submission Date: December 2015

Clinical

4. Submit Week 96 reports and datasets for Studies A4001027 and A4001028.

Report submission: July 2008

5. Conduct a five-year follow-up for subjects in Studies A4001027 and A4001028 for mortality, liver failure, malignancy, myocardial ischemia or infarction and rhabdomyolysis, as well as for infections reported as serious adverse events or qualify as a CDC Category C event.

Final 5 year study report submission: August 2011

6. Conduct and submit a final report for a non-randomized, controlled, observational study to provide additional safety data regarding the incidence of mortality, liver failure, malignancy, myocardial ischemia or infarction, and rhabdomyolysis, as well as for infections that qualify as a CDC Category C event. Follow-up of subjects will be at least every 6 months for a total of 5 years.

Protocol Submission: December 2007

Final Report Submission: June 2016

7. Conduct and submit a study in patients with HIV-1 who are co-infected with hepatitis C and/or B, including some subjects with a Child-Pugh score of C.

Protocol Submission: April 2008

Interim Report Submission: December 2011

Final Report Submission: December 2013

8. Submit Week 48 and Week 96 reports for Study A4001026. Subjects in this study will also be followed for a total of 5 years for mortality, liver failure, malignancy, myocardial ischemia or infarction, rhabdomyolysis, as well as for infections reported as serious adverse events or qualify as a CDC Category C events.

Week 48 interim report submission: October 2007

Week 96 study report submission: November 2008

Final 5 year study report submission: October 2011

Microbiology

9. Perform cell culture combination activity of maraviroc with darunavir and tipranavir, and submit complete study report of these assessments.

Final Report Submission: May 2008

Clinical Pharmacology

10. Conduct a study to evaluate the effect of renal impairment on the pharmacokinetics of maraviroc.

- a) at a dose of 150 mg when combined with a boosted protease inhibitor (e.g., saquinavir/ritonavir) in subjects with mild and moderate renal impairment and subjects with End-Stage Renal Disease (ESRD) that require dialysis.
b) at a dose of 300 mg alone in subjects with severe renal impairment and subjects with end stage renal disease who require dialysis.

Protocol Submission: December 30, 2007

Final Report Submission: December 30, 2008

11. Conduct a study to evaluate the potential for maraviroc metabolite(s) to inhibit CYP2D6 enzymes at a maraviroc dose of 600 mg.

Protocol Submission: December 30, 2007

Final Report Submission: June 30, 2008

12. Conduct a study to evaluate the potential of maraviroc to inhibit P-gp.

Protocol Submission: December 30, 2007

Final Report Submission: June 30, 2008

13. Conduct a study to investigate the potential for maraviroc to induce CP1A2.

Protocol Submission: December 30, 2007

Final Report Submission: June 30, 2008

14. Conduct and submit a clinical study to evaluate the potential for pharmacodynamic interaction between maraviroc and inhibitors of phosphodiesterase type 5 (PDE5).

Protocol Submission: December 2007

Final Report Submission: June 2008

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/s/

Kenny Shade
8/7/2007 01:02:30 PM
CSO



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 31, 2007
To: Debra B. Birkrant, M.D., Director
Division of Antiviral Products
Thru: Solomon Iyasu, M.D., MPH, Director
Division of Surveillance, Research and Communication Support
From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Division of Surveillance, Research and Communication Support
Subject: DSRCS review of proposed Medication Guide
Drug Name(s): Selzentry (maraviroc) Tablets 150 mg and 300 mg
Application Type/Number: N22-128
Applicant/sponsor: Pfizer Incorporated
OSE RCM #: 2007-1653

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INTRODUCTION

The Sponsor submitted a Complete Response Submission for NDA 22-128 Selzentry (maraviroc) Tablets, on July 25, 2007, in response to the Agency's June 20, 2007, Approvable Letter. The Sponsor was notified in the Approvable letter that the Agency was concerned with drug-related hepatotoxicity and requested revised labeling along with a Medication Guide. The Medication Guide was requested under 21 CFR 208 in order to prevent serious adverse effects, inform patients of information concerning risks that could affect their decision to use or continue to use the drug, and/or assure effective use of the drug. DSRCs has been consulted to review the draft Medication Guide.

MATERIAL REVIEWED

We have reviewed the Sponsor's proposed Medication Guide dated July 25, 2007 along with the version of the Full Prescribing Information (FPI) attached to the Approvable letter dated June 20, 2007.

DISCUSSION

See the attached revised Medication Guide (marked up and clean) for our suggested revisions to the Sponsor's draft Medication Guide. We have revised the Medication Guide to be consistent with the Full Prescribing Information (FPI), simplified the language where possible, removed unnecessary information, and ensured that the Medication Guide is in compliance with the regulations as specified in 21 CFR 208.20.

Comments to the review division are **bolded, underlined and italicized.**

CONCLUSIONS AND RECOMMENDATIONS

- The Sponsor's draft Medication Guide has a Flesch-Kincaid Grade Level of 8.8 and a Flesch Reading ease of 58%. Our revisions lowered the reading level to 7.7 (Flesch-Kincaid) and raised the reading ease to 62% (Flesch-Kincaid). All patient materials should be written at an 6th to 8th grade reading level.
- The Medication Guide must be consistent with the information presented in the prescribing information. Add information regarding signs and symptoms of hepatotoxicity and missed dose information to the FPI.
- The Medication Guide must be referenced in the FPI, Highlights section, under "See section 17" and in Section 17, Patient Counseling Information.
- All relevant future changes to the Full Prescribing Information (FPI) should also be reflected in the Medication Guide.

Please let us know if you have any questions.

10 Page(s) Withheld

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 b Draft Labeling

 Deliberative Process

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/s/

Sharon Mills
7/31/2007 04:45:23 PM
DRUG SAFETY OFFICE REVIEWER

Solomon Iyasu
7/31/2007 05:16:24 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Division of Antiviral Products
Office of Antimicrobial Products
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 22-128

Drug: SELZENTRY (maraviroc)

Date: July 31, 2007

To: Leilani V. Kapili, MA, Director, Worldwide Regulatory Affairs and Quality Assurance

Sponsor: Pfizer Inc.

From: Jeff O'Neill, ACRN, Regulatory Health Project Manager, DAVP

Through: Scott Proestel, MD, Medical Officer, DAVP
Jules O'Rear, PhD, Microbiology Team Leader, DAVP
Jenny Zheng, PhD, Clinical Pharmacology Reviewer, DCPB4
Pravin Jadhav, PharmD, Staff Fellow, DCPB4

Concur: Debra Birnkrant, MD, Director, DAVP
Jeffrey Murray, MD, Deputy Director, DAVP
Kellie S. Reynolds, Deputy Director, DCPB4

Subject: Labeling comments

Attached is a copy of the Package Insert and Medication Guide submitted July 25, 2007, with our recommended revisions in Track Changes format. Please also refer to your new drug application (NDA) 22-128, submitted December 20, 2006.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Attached: USPI and Medication Guide

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X Draft Labeling

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Withheld Track Number: Administrative-_____

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/s/

Jeff ONeill
7/31/2007 04:10:43 PM
CSO

Labeling comments for NDA 22128. Hard copy sign off 7/31/07

Debra Birnkrant
7/31/2007 04:37:31 PM
MEDICAL OFFICER
NDA 22-128



MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 22-128
Drug: SELZENTRY (maraviroc)
Date: July 31, 2007
To: Leilani V. Kapili, MA, Director, Worldwide Regulatory Affairs and Quality Assurance
Sponsor: Pfizer Inc.
From: Jeff O'Neill, ACRN, Regulatory Health Project Manager, DAVP
Through: Scott Proestel, MD, Medical Officer, DAVP
Concur: Debra Birnkrant, MD, Director, DAVP
Subject: Clinical Comments

The following clinical comments are in reference to the USPI and Medication Guide submitted July 25, 2007. Please also refer to your new drug application (NDA) 22-128, submitted December 20, 2006.

[REDACTED]

[REDACTED]

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 D Draft Labeling

 Deliberative Process

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/s/

Jeff O'Neill
7/31/2007 04:07:25 PM
CSO

Clinical comments for NDA 22128. Hard copy sign off 7/31/07

Debra Birnkrant
7/31/2007 04:32:25 PM
MEDICAL OFFICER
NDA 22-128

REQUEST FOR CONSULTATION

(Office/Division): FDA/CDER/OSE/DSRCS

FROM (Name, Office/Division, and Phone Number of Requestor): Kenny Shade/OND/Division of Antiviral Drug Products/301-796-0807

DATE July 27, 2007	IND NO. 65,229	NDA NO. 22-128	TYPE OF DOCUMENT MedGuide	DATE OF DOCUMENT July 27, 2007
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NAME OF DRUG SELZENTRY (maraviroc)	PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG Antiviral	DESIRED COMPLETION DATE 8/1/2007
---------------------------------------	--------------------------------	-------------------------------------	-------------------------------------

NAME OF FIRM: Pfizer Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

II. BIOMETRICS

- | | |
|--|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Review of Medication Guide for SELZENTRY (maraviroc)

SIGNATURE OF REQUESTOR Kenny Shade	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Kenny Shade

7/27/2007 02:24:50 PM

MEMORANDUM OF TELECON

DATE: July 20, 2007

APPLICATION NUMBER: NDA 22-128

BETWEEN:

Name: Martha Brumfield
Phone: 212-733-5406
Representing: Pfizer Inc.

AND

Name: John K. Jenkins
Director, Office of New Drugs

SUBJECT: NDA 22-128 Labeling proposals

On Thursday, July 19, 2007 Dr. Jenkins received the following email from Martha Brumfield representing Pfizer Inc.:

“Would it be possible for us to speak by phone tomorrow or Monday for about 15 minutes? I would like to understand your perspective on the labeling proposals being discussed with the Division of Anti-Viral Drug Products regarding our product maraviroc. An approvable letter was issued on 20 June 2007 (copy attached) after an accelerated review based on data in a HIV patient population demonstrating resistance to existing therapies. The Division has communicated that you support inclusion of a black box warning and that this is primarily driven by one recent report of possible hepatotoxicity with allergic features in a subject with confounding factors. Our management is interested in better understanding if this represents a shift in policy regarding what criteria will be applied for a general warning versus a black box. I will make myself available at your convenience. If you prefer to call me, my office number is 212-733-5406 and my cell number is 917-335-9571.”

On Friday, July 20, 2007 Dr. Jenkins spoke to Martha by phone. She was not attempting to negotiate away the box, but rather wanted to better understand our perspectives and whether the “criteria for a box” had changed. Dr. Jenkins informed her that the criteria for a box have not changed and that his understanding was that the division/office concerns were related to one worrisome Hy’s law case in the NDA database (the normal volunteer) of only about 800 patients/volunteers exposed to the drug. This may be a signal of the frequency of the events in broader use. Ms. Brumfield was told we have learned that the best time to manage understanding of drug risks is at the time of initial approval and we feel a box will help to ensure that patients and physicians take this into consideration as they make treatment decisions. It was also noted that many HIV drugs have a box and their drug would not be “singled out” in any way in comparison.

Pfizer plans to resubmit the week of July 23, 2007. Dr. Jenkins was informed by Ms. Brumfield that they had a good discussion with the division early in the week of July 16, 2007. She also noted they just got the CHMP favorable decision yesterday and Dr. Jenkins asked her to share that and the labeling with the division.

Kenny Shade, JD, BSN
Regulatory Health Project Manager

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/s/

Kenny Shade
7/25/2007 01:32:49 PM
CSO

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: Office of Surveillance and Epidemiology (OSE)

Submit to CDER OSE CONSULTS via DFS or email.

FROM: Kenny Shade, Regulatory Health Project Manager
Division of Antiviral Products/301-796-0807

DATE: June 22, 2007

IND NO.

NDA NO.: 22-128

TYPE OF DOCUMENT: OSE consult

DATE OF DOCUMENT: June 14, 2007

NAME OF DRUG: SELZENTRY (maraviroc)

PRIORITY CONSIDERATION: High

CLASSIFICATION OF DRUG: 7030140

DESIRED COMPLETION DATE: June, 2007

NAME OF FIRM: Pfizer Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Healthy volunteer hepatotoxicity case. In a food effect study a 27 year old woman on day 14 dosing developed flu-like symptoms and postural hypotension and was noted to have submaxillary and cervical adenopathy. She was also noted to have a rise in her eosinophil count from 1.1% at baseline to 5.1% on day 14. She developed dizziness, shivering, pruritis, and weakness. Over the next few days she went on to develop a rash later described as an urticarial like rash. Her total bilirubin became elevated (peak 2.3mg/dl) and her AST and ALT were also elevated (peak AST 504 U/L and ALT 393 U/L). Her eosinophils peaked at 10.5%. She was also noted to have an elevated IgE level. A gastroenterology consult was obtained and her findings were considered consistent with drug induced hepatitis. Her maraviroc dosing was discontinued. the subject had a sore throat that began 2 days prior to maraviroc dosing and resolving 12 days prior to her flu-like symptoms.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Kenny Shade
6/22/2007 01:36:43 PM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 20, 2007

From: Stephen M. Grant, M.D.
Scientific Lead, Interdisciplinary Review Team for QT Studies
Division of Cardiovascular and Renal Products /CDER

Through: Norman Stockbridge, M.D., Ph.D.
Division Director, DCRP

To: Kenny Shade, R.N., J.D.
Regulatory Project Manager
Division of Antiviral Products

Subject: QT-IRT consult to review summary data from a reinterpretation of ECGs acquired during a 'thorough QT study'

This memo responds to your email to us dated 18 Jun 2007 regarding summary data from a reinterpretation of ECGs acquired during 'thorough QT' study A4001016 submitted by Pfizer to support under NDA 22-128. The QT-IRT received and reviewed the following materials:

- 13 page Word document containing Pfizer's summary of the data generated by a new reading of ECGs acquired during A4001016

Background

In our previous consult dated 11 May 2007 we noted that the change over time in QTc after administration of moxifloxacin in study A4001016 was unusual. We also noted that the protocol did not stipulate that the ECGs were interpreted by cardiologists blinded to treatment assignment and therefore were concerned that the ECG interpretation could be biased. Additionally, the preclinical studies demonstrated Maraviroc prolonged ventricular repolarization in animals at 8 times the serum concentrations expected after a therapeutic dose in humans.

Your division requested that Pfizer have the ECGs from A4001016 re-read by different cardiologists blinded to subject, treatment group, treatment period, and time.

Sponsor's Submission

The sponsor states "all ECGs were manually randomly blinded to visit date and time, therefore the readers were unable to know the sequence the ECGs were recorded in. All ECGs of a given subject were first read by a single cardiac technician, followed by review by a single cardiologist, to reduce reader variability.

The data obtained from the analysis of the new manually-read dataset are consistent with the previous analysis, within the variability of the data, and confirm the results previously submitted to FDA."

QT-IRT COMMENTS

The key figures are 11-13, which show the placebo and baseline subtracted mean change in QTc after administration of moxifloxacin and three doses of Maraviroc as a function of time.

Figures 11 and 12 show the placebo and baseline subtracted mean change in QTc from manually interpreted ECGs. Although lacking confidence intervals, these figures look similar to the ones generated after the original interpretation of the ECGs.

Figure 13 shows the same parameter but using data from ECGs read by an automatic algorithm and the time course of QTc after moxifloxacin in this figure is similar to the expected, i.e. the largest increase occurs at two hours and steadily declines thereafter to about half maximum at 12 hours.

QT-IRT RECOMMENDATIONS

We understand that you must make a regulatory decision about this application soon.

1. We can not comment on the accuracy of the Pfizer's analysis as we have received only a summary of the data and therefore can not independently assess the analysis.
2. If the Pfizer's summary is an accurate depiction of the results we would accept Pfizer's assertion that assay sensitivity has been demonstrated. The time course of QTc after moxifloxacin is not so unusual as to invalidate the study. It is particularly noteworthy that the "automatically" interpreted ECGs generate a QTc time course that appears within normal.
3. If you choose to accept the sponsor's summary data, we request you submit the data to the QT-IRT so we may independently verify it.
4. If you choose to approve the marketing application, we would recommend you include information about the preclinical studies in the label.

Thank you for requesting our continued input into your review of this NDA. We welcome more discussion with you now and in the future.

Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

MEMORANDUM

To: Kenny Shade, JD, BSN
Division of Special Pathogens and Transplant Products

From: Iris Masucci, PharmD, BCPS
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: June 7, 2007

Re: Comments on draft labeling for maraviroc tablets
NDA 22-128

We have reviewed the proposed label for maraviroc (FDA version dated 5/21/07 and sponsor's response dated 6/4/07) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

GENERAL COMMENTS

- Please ensure that Highlights and Contents are properly formatted (e.g., 8-point font, 2-column format) for review to ensure that Highlights meets the ½-page maximum length requirement.
- A recent joint effort between FDA and the Institute for Safe Medication Practices discourages using abbreviations in all medical communication, including prescription drug labeling, that may potentially result in medication errors. Among the recommendations is not to use Latin abbreviations (e.g., QD, BID) in labels; instead, we should use "once daily" and "twice daily." Another recommendation is to use spaces, not dashes, between the strength and the unit when expressing drug doses (e.g., use "150 mg" instead of "150-mg"). Please make these changes throughout the label.
- The cross-references in the Full Prescribing Information (FPI) are not in the proper format. The preferred presentation is to reference the main section name, with the appropriate subsection number in parentheses [e.g., "*See Clinical Pharmacology (12.3)*" and not "*See Pharmacokinetics (12.3)*"]. Additionally, the entire cross-reference should be italicized. Please correct throughout the label.
- When subheadings are used within numbered subsections, the preferred formatting for the titles is italicizing and/or underlining. If possible, bolded titles should be reserved for numbered sections or subsections.

- This label often refers to studies as “Phase 1, 2, or 3.” The use of these terms is being discouraged in labels because these they are not very descriptive. Instead, we should describe the nature of the study, as appropriate.
- The clinical studies described in the label are identified using names such as “A4001027.” In general, internal company study titles should not be used in labeling because they can be confusing to the reader. Instead, the studies can be identified using acronyms (e.g., MOTIVATE-1) or can simply be called “Studies 1 and 2” or “Studies A and B.”
- Will the patient package insert be attached to the label as one long document or will it accompany the label? Either way is acceptable under the PLR. If it will be attached, then it should be given a subsection number (e.g., 17.2) and be listed in Contents. If it will be separate, then it should not be listed in Contents and the first line under “17 Patient Counseling Information” should refer the reader to the PPI, but without a subsection number in parentheses.

HIGHLIGHTS

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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 b Draft Labeling

 Deliberative Process

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/s/

Melissa Furness
6/19/2007 02:18:44 PM
CSO
Signing for Iris Masucci



Food and Drug Administration
Division of Antiviral Products
Office of Antimicrobial Products
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 22-128
Drug: (maraviroc)
Date: June 12, 2007
To: Leilani V. Kapili, MA
Sponsor: Pfizer Inc.
From: Kenny Shade, JD, BSN
Through: Scott Proestel, MD
Concur: Katherine Laessig, MD
Subject: Review Team Comments

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-128 submitted December 20, 2006.

Review Team Comments

1. We recommend expedited 15-day reporting of the following events during the postmarketing period: liver-related deaths and liver failure, fatal and nonfatal MIs, all non-AIDS defining malignancies.

[Redacted]

[Redacted]

3. A copy of all healthcare provider and patient educational materials should be submitted to the Agency

[Redacted]

4. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions.

GENERAL COMMENTS

- Please ensure that Highlights and Contents are properly formatted (e.g., 8-point font, 2-column format) for review to ensure that Highlights meets the ½-page maximum length requirement.
- A recent joint effort between FDA and the Institute for Safe Medication Practices discourages using abbreviations in all medical communication, including prescription drug labeling, that may potentially result in medication errors. Among the recommendations is not to use Latin abbreviations (e.g., QD, BID) in labels; instead, we should use “once daily” and “twice daily.” Another recommendation is to use spaces, not dashes, between the strength and the unit when expressing drug doses (e.g., use “150 mg” instead of “150-mg”). Please make these changes throughout the label.
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- This label often refers to studies as “Phase 1, 2, or 3.” The use of these terms is being discouraged in labels because these they are not very descriptive. Instead, we should describe the nature of the study, as appropriate.
- The clinical studies described in the label are identified using names such as “A4001027.” In general, internal company study titles should not be used in labeling because they can be confusing to the reader. Instead, the studies can be identified using acronyms (e.g., MOTIVATE-1) or can simply be called “Studies 1 and 2” or “Studies A and B.”
- Will the patient package insert be attached to the label as one long document or will it accompany the label? Either way is acceptable under the PLR. If it will be attached, then it should be given a subsection number (e.g., 17.2) and be listed in Contents. If it will be separate, then it should not be listed in Contents and the first line under “17 Patient Counseling Information” should refer the reader to the PPI, but without a subsection number in parentheses.

HIGHLIGHTS

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8 Draft Labeling

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Kenny Shade, JD, BSN
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

Kenny Shade
6/19/2007 01:23:18 PM
CSO

Kathrine Laessig
6/19/2007 01:31:33 PM
MEDICAL OFFICER

MEMORANDUM**Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
WO 22, Mailstop 4447, HFD-420
Center for Drug Evaluation and Research**

To: Debra Birnkrant, MD
Director, Division of Antiviral Products
HFD-530

Through: Kristina C. Amwine, PharmD., Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Linda M. Wisniewski, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: June 1, 2007

OSE Review # 2007-1131, Selzentry (Maraviroc Tablets)
400 mg
NDA# 22-128

This memorandum was written in response to a request from the Division of Antiviral Products (HFD-530), to review the proprietary name Selzentry. This is the third proprietary name submitted for Maraviroc Tablets. The sponsor initially submitted the name Celsentri to DMETS for review. However DDMAC objected to the use of the proposed name Celsentri, because it overstates the efficacy of the drug. Because of its potential to look similar to the drug name, Celontin, DMETS did not recommend the use of the proprietary name, Celsentri (OSE Consult 06-0188). DMETS re-reviewed the name Celsentri in OSE Consult 2007-245 and concerns regarding the potential for confusion with Celontin were reiterated. Container labels, carton and insert labeling were reviewed in OSE Consult 2007-245. Revised labels and labeling were not submitted for review and comment.

The sponsor subsequently submitted three additional proprietary names for consideration, Zelsentry, Selzentry, and Csentri. DMETS did not recommend use of the proprietary name Zelsentry because of its potential to look similar to the drug product, Zileuton. This information was conveyed via email to the Division on May 31, 2007. Since the first choice was eliminated, DMETS reviewed the proposed proprietary name, Selzentry (second choice).

Limited time was available to complete a comprehensive analysis of the proprietary name, Selzentry because of the PDUFA date of June 20, 2007. Thus, due to the high priority nature of this review, the routine name analysis was not performed. The DMETS' safety evaluator was only able to conduct a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Selzentry to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The proposed name was not discussed during a CDER Expert Panel Discussion, and CDER Prescription Studies were not conducted regarding Selzentry.

¹ MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

In reviewing the proprietary name Selzentry, the names identified to have visual and phonetic similarity to Selzentry are Centany, Cellcept, Serentil, Selagine, Survanta, Seltzer, Serevent, Sulfatrim, and Serpanray. However, as noted above, due to time constraints, this list may not be inclusive of all names with look-alike and/or sound-alike potential.

In the analysis of the nine names identified, it was determined that all nine names would not pose a risk of confusion for the following reasons:

- Centany lacks convincing sound-alike properties, in addition to having differentiating product characteristics, such as usual dose (150 mg, 300 mg, and 600 mg vs. small amount), dosage form (tablets vs. ointment), frequency of administration (twice daily vs. three times daily), product strength (150 mg and 300 mg vs. 2%), and route of administration (oral vs. topical).
- Cellcept lacks convincing sound-alike properties, in addition to having differentiating product characteristics, such as usual dose (150 mg, 300 mg, or 600 mg vs. 1 g, 1.5 g, or 600 mg/m²) and product strength (150 mg and 300 mg vs. 250 mg and 500 mg).
- Serentil was removed from the US market in 2004 and there are no generics available.
- Selagine is an ingredient in herbal supplements and not marketed as a separate drug product.
- Survanta lacks convincing sound-alike properties, in addition to having differentiating product characteristics, such as dose (150 mg, 300 mg, and 600 mg vs. 2.6 mL to 8 mL), dosing frequency (twice daily vs. every six hours), product strength (150 mg and 300 mg vs. 25 mg/mL), route of administration (oral vs. intratracheal), and patient population (patients able to swallow tablets vs. premature infants).
- Seltzer was not reviewed further because it is plain water into which carbon dioxide gas has been dissolved and not a drug product that would be prescribed.
- Serevent lacks convincing sound-alike properties, in addition to having differentiating product characteristics, such as usual dose (150 mg, 300 mg, and 600 mg vs. one inhalation or 50 mcg), product strength (150 mg and 300 mg vs. 0.046 mg/inhalation), and route of administration (oral vs. inhalation).
- Sulfatrim lacks convincing sound-alike properties, in addition to having differentiating product characteristics, such as usual dose (150 mg, 300 mg, and 600 mg vs. 160 mg/800 mg, [8 mg/40 mg]/kg) and product strength (150 mg and 300 mg vs. [200 mg/40 mg]/5 mL, 800 mg/160 mg, and 400 mg/80 mg).
- Serpanray, although discontinued, is still available as a generic with the same active ingredient, however, following review there is minimal sound-alike properties and there are numerous differentiating product characteristics such as, usual dose (150 mg, 300 mg, and 600 mg vs. 0.1 mg to 1 mg), frequency of administration (twice daily vs. once daily), and product strength (150 mg and 300 mg vs. 0.1 mg and 0.25 mg).

Based on the information available at this time, DMETS has not identified any proprietary names that have orthographic or phonetic similarity to Selzentry at this time. The Division of Drug Marketing, Advertising, and Communications has no objections to the use of the proprietary name Selzentry from a promotional perspective. If the approval of this application is delayed beyond 90 days from the signature date of document, a complete evaluation of the name should be conducted. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

DMETS will not provide comment on the third name Csentri because we find Selzentry acceptable at this time. DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Tanya Clayton, Project Manager, at 301-796-0871.

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/s/

Linda Wisniewski
6/12/2007 10:05:07 AM
DRUG SAFETY OFFICE REVIEWER

Kristina Arnwine
6/12/2007 10:14:08 AM
DRUG SAFETY OFFICE REVIEWER
Acting Team Leader

Denise Toyer
6/12/2007 04:00:04 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/12/2007 04:34:22 PM
DRUG SAFETY OFFICE REVIEWER



NDA 22-128

INFORMATION REQUEST LETTER

Pfizer Inc
Attention: Leilani Kapili, Associate Director
50 Pequot Trail
New London, CT 06320

Dear Ms. Kapili:

Please refer to your December 20, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for maraviroc tablets. We also refer to your amendments dated April 19, 2007 and June 1, 2007.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following information requests. Please send your responses as soon as possible so that we may complete our review.

1. Please confirm that Tables 2.3.S.2-23 and 2.3.P.2.3-24 describe the design space for the drug substance and the drug product manufacturing processes, respectively.
2. The bottle and carton labels will be acceptable for commercial use when the agreed-upon proprietary name is inserted on the labels using the same font, font size relative to the non-proprietary name, and layout as were submitted originally in the NDA. Please confirm that you will use this approach for finalizing the labels.

If you have any questions, call Amy Bertha, Project Manager, at (301) 796-1647.

Sincerely,

Elaine Morefield, Ph.D.
Director
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Elaine Morefield
6/11/2007 05:04:04 PM



Food and Drug Administration
Division of Antiviral Products
Office of Antimicrobial Products
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 22-128
Drug: Maraviroc
Date: June 6, 2007
To: Leilani V. Kapili, MA
Sponsor: Pfizer Inc.
From: Kenny Shade, JD, BSN
Through: Scott Proestel, MD
Stephen Miller, PhD
Concur: Katherine Laessig, MD
Subject: Review Team Comments

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-128 submitted December 20, 2006 and your email sent May 29, 2007 .

Review Team Comments

1. We understand that the EMEA is recommending a contraindication statement based upon their guidance document, "Public Statement On The Allergenic Potency Of Herbal Medicinal Products Containing Soya Or Peanut Protein." We have evaluated the likely amount of soya protein that could be present in maraviroc tablets because soya lecithin is a minor component of the film coat. Given the limits on hexane insoluble material in the US National Formulary monograph for lecithin, the use of soya lecithin in FDA-approved oral drugs (CDER's Inactive Ingredients Database shows soybean lecithin at up to 20 mg/capsule), and the current approach to lecithin in our regulations (21CFR184.1400), we believe that the allergenicity risk is adequately addressed by listing "soya lecithin" in the package insert. However, if you wish to include the EMEA-recommended contraindication for purposes of harmonization of labeling, that would also be acceptable to us.

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Kenny Shade

Kenny Shade, JD, BSN
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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Kenny Shade
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CSO

Kathrine Laessig
6/18/2007 10:17:52 AM
MEDICAL OFFICER



Food and Drug Administration
Division of Antiviral Products
Office of Antimicrobial Products
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 22-128
Drug: (maraviroc)
Date: June 1, 2007
To: Leilani V. Kapili, MA
Sponsor: Pfizer Inc.
From: Kenny Shade, JD, BSN
Through: Lisa Naeger, PhD
Scott Proestel, MD
Concur: Katherine Laessig, MD
Julian O'Rear, PhD
Subject: Microbiology Comments

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-128 submitted December 20, 2006 and to your email sent on May 29, 2007 requesting clarification.

Microbiology Comments

- Tropism, section 12.4: number of failures and changes in CD4 count.
- What criteria for failure were used to arrive at 172 failures in 1027/1028?

RESPONSE:

Subjects were censored from the analysis if they discontinued with ≤ 400 copies/mL serum HIV-1 RNA or if they discontinued with > 400 copies/mL between Baseline and Week 4 or if they discontinued between Baseline and Week 8 with at least $0.5 \log_{10}$ decrease and no rebound (previous $\geq 2 \log_{10}$ decrease with $1 \log_{10}$ increase) (Appendix). Forty-nine and thirty-nine subjects were censored from the analysis of studies 1027 and 1028, respectively.

In an as-treated outcome analysis using the censored dataset and the protocol-defined definition of treatment failure

Table A. Outcome by Treatment Arm in Study 1027 censored (n=536)

	QD (n=209)	BID (n=218)	Placebo (n=109)
Treatment failure	49 (23%)	56 (26%)	59 (54%)
No failure and VL>400	30 (14%)	16 (7%)	14 (13%)

copies/mL			
No failure and VL≤400 copies/mL	119 (57%)	139 (64%)	30 (28%)
DC VL>400 copies/mL	11 (5%)	7 (3%)	6 (6%)

Table B. Outcome by Treatment Arm in Study 1028 censored (n=426)

	QD (n=164)	BID (n=178)	Placebo (n=84)
Treatment failure	32 (20%)	35 (20%)	48 (57%)
No failure and VL>400 copies/mL	23 (14%)	19 (11%)	11 (13%)
No failure and VL≤400 copies/mL	99 (60%)	114 (64%)	20 (24%)
DC VL>400 copies/mL	10 (6%)	10 (6%)	5 (6%)

So treatment failures on MVC using PDTF definition = 172

- Were CD4 counts re-calculated at time of failure per the criteria above?

RESPONSE:

Yes, protocol defined treatment failures from censored dataset. Subjects in the maraviroc arms failing with CXCR4- or dual/mixed tropic virus (n=101) had less of a median increase in CD4⁺ cell counts from baseline (+27 cells/mm³) (mean = 45 cells/mm³) than those subjects failing with CCR5-tropic virus (n=49) (+88 cells/mm³) (mean =119 cells/mm³).

- Clinical Studies, Tables 9 and 10
- OSS numbers changed by 1 (maraviroc/plc: 57/35 to 56/36 and 136/44 to 137/43). Please clarify the reason for changes (original numbers consistent with SCE Table 13.5.1)

RESPONSE:

The numbers were changed based on the resistance dataset, but since the percentages don't change, we agree to keep your originally proposed numbers.

APPENDIX

Censored:

- D/C While Suppressed
- Blank
- D/C Before Achieve Viral Suppression:
 - Subjects D/C between Week 0-4
 - Subjects with HIV RNA data only through week 8 censored if achieve at least 0.5 log decrease and no rebound (previous ≥2 log decrease with 1 log increase)

Subjects Censored from Study 1027: D/C Before Achieve Viral Suppression:

PID	TRT
A4001027 10010017	bid
A4001027 10130004	plc
A4001027 10170005	bid
A4001027 10200018	bid
A4001027 10270005	qd
A4001027 10370009	bid
A4001027 10410012	bid

A4001027 10480045	qd
A4001027 10530008	qd
A4001027 10580014	qd
A4001027 10630003	qd
A4001027 10680019	plc
A4001027 10680020	qd
A4001027 10810014	bid
A4001027 10900025	bid
A4001027 11010015	qd
A4001027 11060006	qd
A4001027 11090016	qd
A4001027 11110018	qd
A4001027 11310010	bid
A4001027 10220015	plc

Subjects Censored from Study 1028: D/C Before Achieve Viral Suppression:
--

<u>PID</u>	<u>TRT</u>
A4001028 10440012	bid
A4001028 10510034	plc
A4001028 10820032	plc
A4001028 10890014	qd
A4001028 11140006	plc
A4001028 11230001	bid
A4001028 11400019	qd
A4001028 11610005	plc
A4001028 11710003	qd
A4001028 11740005	qd
A4001028 11940011	qd
A4001028 11980001	plc

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Kenny Shade, JD, BSN
 Regulatory Project Manager
 Division of Antiviral Products
 Center for Drug Evaluation and Research
 Food and Drug Administration

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/s/

Kenny Shade
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CSO

Kathrine Laessig
6/1/2007 02:11:46 PM
MEDICAL OFFICER



Food and Drug Administration
Division of Antiviral Products
Office of Antimicrobial Products
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 22-128
Drug: (maraviroc)
Date: May 31, 2007
To: Leilani V. Kapili, MA
Sponsor: Pfizer Inc.
From: Kenny Shade, JD, BSN
Through: Jenny Zheng, PhD
Scott Proestel, MD
Concur: Katherine Laessig, MD
Kellie Reynolds, PharmD
Subject: Clinical Pharmacology Proposed Post Marketing Commitments

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-128 submitted December 20, 2006.

1. Conduct a study to evaluate the effect of renal impairment on the pharmacokinetics of maraviroc:
 - (a) at a dose of 150 mg when combined with a boosted protease inhibitor (e.g., saquinavir/ritonavir) in subjects with mild, moderate, and severe renal impairment and subjects with End-Stage Renal Disease (ESRD) that require dialysis.
 - (b) at a dose of 300 mg alone in subjects with severe renal impairment.

Protocol submission: December 30, 2007
Final report submission: December 30, 2008

2. ~~_____~~
~~_____~~ Conduct a study to evaluate the potential for maraviroc metabolite(s) to inhibit CYP2D6 enzymes in vivo at a maraviroc dose of 600 mg ~~_____~~
~~_____~~

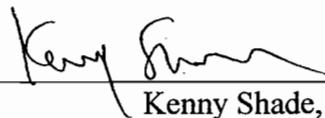
Protocol submission: December 30, 2007
Final report submission: June 30, 2008

3. Conduct a study to evaluate the potential of maraviroc to inhibit P-gp.

Protocol submission: December 30, 2007

Final report submission: _____ 30, 2008

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Kenny Shade, JD, BSN
Regulatory Project Manager
Division of Antiviral Products
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Kenny Shade
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Kathrine Laessig
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Food and Drug Administration
Division of Antiviral Products
Office of Antimicrobial Products
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 22-128
Drug: maraviroc
Date: May 24, 2007
To: Leilani V. Kapili, MA
Sponsor: Pfizer Inc.
From: Kenny Shade, JD, BSN
Through: Scott Proestel, MD
Lisa Naeger, PhD
Concur: Katherine Laessig, MD
Julian O'Rear, PhD
Subject: Proposed Post Marketing Commitments

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-128 submitted December 20, 2006.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your postmarketing study commitments specified in your submission dated May 10, 2007. These commitments, along with any completion dates agreed upon, are listed below.

1. Submit Week 48 and Week 96 reports and datasets for Studies A4001027 and A4001028. Subjects in these studies will also be followed for at least 5 years for mortality, liver failure, malignancy, myocardial ischemia or infarction, and rhabdomyolysis, as well as for infections considered at least moderate in severity or qualify as a CDC Category C event.

Protocol submission: Study ongoing [Pfizer please provide exact date of protocol submission]
Final report submission: [Please propose date]

We acknowledge your commitment to participate in the Antiretroviral Pregnancy Registry.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

or infarction, and rhabdomyolysis, as well as for infections considered at least moderate in severity or qualify as a CDC Category C event.

Protocol submission: [Pfizer please provide exact date of protocol submission]

Final report submission: [Please propose date]

Microbiology

7. Perform cell culture combination activity assessments of maraviroc with darunavir and tipranavir, and submit complete study report of these assessments _____

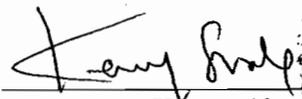
Final report submission: _____

id

In addition we are requesting the maraviroc phenotype and genotype for all subjects who fail on maraviroc with CCR5-tropic virus in studies A4001026, A4001027, and A4001028 to be included with the traditional approval application.

Please note the Clinical Pharmacology Post Marketing Commitments will be sent in a separate letter at a later date.

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Kenny Shade, JD, BSN
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
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/s/

Kenny Shade
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CSO

Kathrine Laessig
5/24/2007 03:22:53 PM
MEDICAL OFFICER



NDA 22-128

INFORMATION REQUEST LETTER

Pfizer Inc
Attention: Leilani Kapili, Associate Director
50 Pequot Trail
New London, CT 06320

Dear Ms. Kapili:

Please refer to your December 20, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Maraviroc tablets. We also refer to your amendment dated April 19, 2007.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Alternatively, if you are not in agreement, a teleconference to discuss these requests could be held on May 31, 2:30-3:30 pm, or at a mutually agreed upon time.

- 1. }
- }
- :
- :

[Redacted line]

[Redacted line]

- 2. For increased clarity, revise the units for roll force in the Design Space Tables 3.2.P.2.3-16 and 3.2.P.2.3-24 to capture that Design Space is in terms of roll force per unit length (kN/cm) rather than in terms of roll force (kN). We acknowledge that your response to Question 12 of the March 29, 2007 IR letter states that Design Space is in terms of roll force per unit length and concur that

this is scale invariant; however roll force is not, as supported by review of roller compactor scale-up literature.

If you have any questions, call Amy Bertha, Regulatory Health Project Manager, at 301-796-1647.

Sincerely,

{See appended electronic signature page}

Elaine Morefield, Ph.D.
Director
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Elaine Morefield
5/24/2007 09:29:49 AM



NDA 22-128

Pfizer Inc.
Attention: Leilani V. Kapili, MA
Director
Worldwide Regulatory Affairs and Quality Assurance
50 Pequot Avenue
New London, CT 06320
USA

Dear Ms. Kapili:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CELSENTRI® (maraviroc).

We also refer to your submission dated June 6, 2006 (serial number 225), containing a proposal for the proprietary name CELSENTRI.

A review by the Division of Medication Errors and Technical Support (DMETS) of your submission has been completed, resulting in the following comments:

- **CELSENTRI** – DMETS does not recommend the use of the proprietary name Celsentri. In reviewing the proprietary name, the primary concern relates to look-alike confusion with the marketed product, CELONTIN. DMETS also has recommendations on label and labeling improvements in the interest of patient safety.
- CELONTIN contains methsuximide and is indicated for the treatment of petit mal seizures that are refractory to other drugs. CELONTIN and CELSENTRI both begin with “Cel” and may appear similar in length (8 letters vs. 9 letters). The endings (“ontin” and “entri”) may resemble one another when scripted. Although CELSENTRI contains the letter “s” in the middle of the name, this can be easily overlooked as the remaining letters are orthographically similar to CELONTIN.
- CELONTIN and CELSENTRI overlap in both strengths (150 mg and 300 mg). Additionally, they overlap in route of administration (oral), usual dose (300 mg), total daily dose (300 mg and 600 mg), and they will both be available as solid oral dosage forms (tablets/capsules). Furthermore, CELONTIN and CELSENTRI share the same manufacturer (Pfizer). Conversely, CELONTIN and CELSENTRI differ in indication for use (seizures vs. HIV), and frequency of administration (once daily vs. twice daily). Despite a difference in frequency of administration (once daily vs. twice daily), DMETS

has learned from post-marketing experience that the dosing frequency may not be enough to prompt practitioners as to what the product is, if the names look similar when scripted (e.g., Reminyl [dosed BID] and Amaryl [dosed QD], and Amicar [dosed every 6 to 8 hours] and Omacor [dosed QD or BID]). Thus, a written prescription for "CELSENTRI 300 mg po BID" could be misinterpreted as "CELONTIN 300 mg po BID". The difference in frequency may not be sufficient to differentiate the names because of the overlapping strength and strong orthographic similarities.

- Both CELONTIN and CELSENTRI begin with "Cel", thus, the potential exists for both products to be placed side-by-side on pharmacy shelves. Products are generally stored by either tradename, generic name, or manufacturer. In any of these cases, the products will be in close proximity to one another. Since both products are made by Pfizer, the labeling looks similar. Similar product appearance and similar storage conditions could lead to shelf selection errors. Additionally, the potential for selection errors is compounded by their overlapping strengths (150 mg and 300 mg).
- If CELONTIN is mistakenly dispensed in place of CELSENTRI, a patient will experience a delay in HIV treatment, which may affect the patient's health. If a patient receives CELSENTRI in place of CELONTIN, the patient will unnecessarily be exposed to an HIV drug and may experience negative side effects from the medication. Furthermore, the patient will be at an increased risk of seizures, which may be harmful to the patient or others depending upon the situation when the patient experiences the seizure.
- Due to the strong orthographic similarities, overlapping product characteristics (strength, usual dose, total daily dose, route of administration, dosage form), and similar corporate dress, it is DMETS position that these products may not safely co-exist in the marketplace.

At this time we request that you submit alternate proprietary names for our review. If you have any questions, call Kenny Shade, Regulatory Health Project Manager, at 301-796-0807.

Sincerely,

Anthony DeCicco
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

Tony DeCicco
5/16/2007 08:52:09 AM

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22; Mail Stop 4447)

DATE RECEIVED: 1/29/07	DESIRED COMPLETION DATE: 5/1/07	OSE REVIEW #:
DATE OF DOCUMENT: 12/20/06	PDUFA DATE: 6/20/07	2007-245

TO: Debra Birnkrant, MD
Director, Division of Anti-Viral Products
HFD-530

THROUGH: Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Felicia Duffy, RN, BSN, MSED, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: Celsentri (Maraviroc) Tablets 150 mg and 300 mg	SPONSOR: Pfizer
NDA #: 22-128	

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Celsentri. Due to the strong orthographic similarities, overlapping product characteristics (strength, usual dose, total daily dose, route of administration, dosage form), and similar corporate dress to Celontin. DMETS reiterates its position that Celsentri and Celontin may not safely co-exist in the marketplace.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC does not recommend the use of the proprietary name from a promotional perspective for the following reasons:

"DDMAC objects to the proposed trade name Celsentri because it overstates the efficacy of the drug product. When pronounced, the proposed trade name sounds like "Cell Sentry." A sentry is defined as a "guard, watch [especially] a soldier standing guard at a point of passage" (www.m-w.com accessed 6/19/06). Literally, the proposed trade name translates to mean "cell guard" which may misleadingly suggest maraviroc is a preventative or prophylactic therapy to protect people from being infected with HIV, spreading the virus to others, or that maraviroc protects "healthy" cells from being infected with HIV. However, maraviroc is indicated for the treatment of HIV-1 infection (implying that the patients are already infected with HIV). Given our limited information regarding the indication and in absence of substantial evidence to support that maraviroc produces a protective/preventative effect, the proposed trade name, Celsentri, is misleading.

Please note that 21 CFR 201.10(c)(3) states that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(6)(i)]."

The Division did not agree with DDMAC's assessment of the proprietary name, and asked DMETS to conduct a safety review of the proprietary name, Sterox.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence forwarded to the sponsor pertaining to this review. If you have further questions or need clarifications, please contact Tanya Clayton, Project Manager, at 301-796-871.

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; WO22; Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY, LABEL, AND LABELING NAME REVIEW

DATE OF REVIEW: February 13, 2007

NDA #: 22-128

NAME OF DRUG: **Celsentri**
(Maraviroc) Tablets
150 mg and 300 mg

NDA SPONSOR: Pfizer

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Viral Products, for re-review of the proprietary name "Celsentri", regarding potential name confusion with other proprietary or established drug names. The proposed proprietary name, Celsentri, was found unacceptable by DMETS in a review dated August 6, 2006 (OSE review 06-0188) due to the potential for look-alike confusion with the currently marketed product, Celontin, which is manufactured by the same sponsor. Container labels, carton, and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Celsentri (maraviroc) is a new drug application indicated for treatment-experienced patients infected with CCR5-tropic HIV-1 infection. Celsentri must be given in combination with other antiretroviral agents. The recommended dose is 300 mg twice daily, but adjustments are recommended based on the patient's concomitant medications (see chart below). Celsentri will be available as 150 mg and 300 mg tablets in 30 and 60 count bottles.

Concomitant Medications	CELSENTRI Dose
CYP3A4 inhibitors including: <ul style="list-style-type: none">• protease inhibitors (except tipranavir/ritonavir)• delavirdine• ketoconazole, itraconazole, clarithromycin, nefazadone, telithromycin	150mg twice daily
CYP3A4 inducers (without a CYP3A4 inhibitor) including: <ul style="list-style-type: none">• efavirenz and nevirapine• rifampin and rifabutin,	600mg twice daily
Other concomitant medications, including all other antiretrovirals including tipranavir/ritonavir	300mg twice daily

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II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Celsentri to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Celsentri. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC does not recommend the use of the proprietary name from a promotional perspective for the following reasons:

"DDMAC objects to the proposed trade name Celsentri because it overstates the efficacy of the drug product. When pronounced, the proposed trade name sounds like "Cell Sentry." A sentry is defined as a "guard, watch [especially] a soldier standing guard at a point of passage" (www.m-w.com accessed 6/19/06). Literally, the proposed trade name translates to mean "cell guard" which may misleadingly suggest maraviroc is a preventative or prophylactic therapy to protect people from being infected with HIV, spreading the virus to others, or that maraviroc protects "healthy" cells from being infected with HIV. However, maraviroc is indicated for the treatment of HIV-1 infection (implying that the patients are already infected with HIV). Given our limited information regarding the indication and in absence of substantial evidence to support that maraviroc produces a protective/preventative effect, the proposed trade name, Celsentri, is misleading.

Please note that 21 CFR 201.10(c)(3) states that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(6)(i)]."

The review Division was informed of DDMAC's objection to the name, Celsentri. However, the Division disagrees with DDMAC and requested DMETS continue its safety review of the

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemiKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

proprietary name.

2. The Expert Panel identified a total of nine proprietary names that were thought to have potential for confusion with Celsentri and were not evaluated in the previous review.

B. PRESCRIPTION STUDY ANALYSIS

Prescription studies were not repeated for this review, as they were conducted in the previous Celsentri review (OSE review #06-0188, section IIB).

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, "Celsentri", a total of nine names were thought to have the potential to either sound or look similar to Celsentri. These names include Alconeprin, Alfenta, Alustra, Cilastatin, Celontin, Centany, Elestrin^{***}, and Lucentis.

Of these nine names, eight names (Alconeprin, Alfenta, Alustra, Cilastatin, Centany, Elestrin^{***}, and Lucentis) were not reviewed further due to lack of convincing look-alike and/or sound-alike similarities with Celsentri in addition to differentiating product characteristics which may include one or more of the following: indication for use, product strength, usual dosage, route of administration, frequency of administration, dosage form, prescriber population, patient population, storage conditions, product unavailability, and/or area of marketing.

The remaining product to be reviewed is listed in Table 1 (see below), along with the dosage forms available and usual dosage. Please note, this is the same name DMETS found in the first review when Celsentri was an IND. However, product characteristics changed since to IND review that may further increase the potential for confusion between these two drug products.

As an IND, Celsentri was proposed to be available in one strength (150 mg) dosed twice daily. The NDA for Celsentri now proposes two strengths, 150 mg and 300 mg. The recommended dose for Celsentri is 300 mg by mouth twice daily; however, the dose may be adjusted due to potential drug interactions with other antiretroviral medications. Thus, the dose may be 150 mg twice daily, 300 mg twice daily or 600 mg twice daily, depending on what other antiretroviral medications are administered. These additional product characteristics have led DMETS to re-review Celsentri and Celontin.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Celsentri	Maraviroc Tablets: 150 mg and 300 mg	150 mg, 300 mg, or 600 mg by mouth twice daily depending upon which other antiretrovirals are administered	
Celontin	Methsuximide Capsules: 150 mg and 300 mg	300 mg to 1.2 grams by mouth once daily.	LA

*Frequently used, not all-inclusive.
**LA (look-alike), SA (sound-alike)

Celontin contains methsuximide and is indicated for the treatment of petit mal seizures that are refractory to other drugs. Celontin and Celsentri both begin with "Cel" and may appear similar in length (8 letters vs. 9 letters). The endings ("ontin" and "entri") may resemble one another when scripted (see example on page 5). Although Celsentri contains the letter "s" in the middle of the name, this can be easily overlooked as the remaining letters are orthographically similar to Celontin.

***** NOTE:** This review contains confidential and proprietary information that should not be released to the public.***

Celsentri
Celontin

Celontin and Celsentri now overlap in both strengths (150 mg and 300 mg) as opposed to previously overlapping in only one strength. Additionally, both drugs overlap in route of administration (oral), usual dose (300 mg), total daily dose (300 mg, 600 mg, or 1200 mg), and they will both be available as solid oral dosage forms (tablets/capsules). Furthermore, Celontin and Celsentri share the same sponsor (Pfizer). Conversely, Celontin and Celsentri differ in indication for use (seizures vs. HIV), and frequency of administration (once daily vs. twice daily).

Celontin 300mg
#60
† po BID

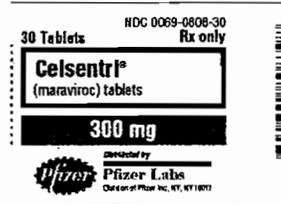
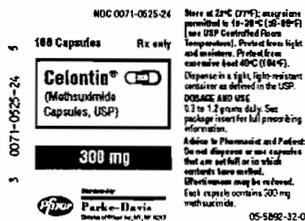
Celsentri 300mg
#60
† po QD

Celontin 150mg
#30
† po QD

Celsentri 150mg
#30
† po BID

Despite a difference in frequency of administration (once daily vs. twice daily), DMETS has learned from post-marketing experience that the dosing frequency may not be enough to prompt practitioners as to what the product is, if both names look similar when scripted (e.g., Reminyl [dosed BID] and Amaryl [dosed QD], and Amicar [dosed every 6 to 8 hours] and Omacor [dosed QD or BID]). Thus, a written prescription for "Celsentri 300 mg po BID" can be misinterpreted as "Celontin 300 mg po BID". The differences in frequency may not be sufficient to differentiate the names because of the overlapping strength and strong orthographic similarities.

Both Celontin and Celsentri begin with "Cel", thus, the potential exists for both products to be placed side-by-side on pharmacy shelves. Products are generally stored by either tradename, generic name, or sponsor. In any of these cases, the products will be in close proximity to one another. Since both products are made by Pfizer, the labeling looks similar (see below). Similar product appearance as illustrated below and similar storage conditions could lead to shelf selection errors. Additionally, the potential for selection errors is compounded by their overlapping strengths (150 mg and 300 mg).



If Celontin is mistakenly dispensed in place of Celsentri, a patient will experience a delay in HIV treatment, which may affect the patient's quality of life. If a patient receives Celsentri in place of Celontin, the patient will unnecessarily be exposed to an HIV drug and may experience negative side effects from the medication. Furthermore, the patient will be at an increased risk of seizures, which may be harmful to the patient or others depending upon the situation when the patient

experiences the seizure.

Due to the strong orthographic similarities, overlapping product characteristics (strength, usual dose, total daily dose, route of administration, dosage form), and similar corporate dress, DMETS reiterates its position that these products may not safely co-exist in the marketplace.

III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proprietary name, Celsentri. In reviewing the proprietary name, the primary concern continues to relate to look-alike confusion with the marketed product, Celontin. DMETS also has recommendations on label and labeling improvements in the interest of patient safety.

Celontin contains methsuximide and is indicated for the treatment of petit mal seizures that are refractory to other drugs. Celontin and Celsentri both begin with "Cel" and may appear similar in length (8 letters vs. 9 letters). The endings ("ontin" and "entri") may resemble one another when scripted (see example on page 5). Although Celsentri contains the letter "s" in the middle of the name, this can be easily overlooked as the remaining letters are orthographically similar to Celontin.

Celsentri
Celontin

Celontin and Celsentri now overlap in both strengths (150 mg and 300 mg) as opposed to previously overlapping in only one strength. Additionally, both drugs overlap in route of administration (oral), usual dose (300 mg), total daily dose (300 mg, 600 mg, or 1200 mg), and they will both be available as solid oral dosage forms (tablets/capsules). Furthermore, Celontin and Celsentri share the same sponsor (Pfizer). Conversely, Celontin and Celsentri differ in indication for use (seizures vs. HIV), and frequency of administration (once daily vs. twice daily).

Celsentri 300mg
#60
† po BID

Celontin 300mg
#60
† po QD

Celontin 150mg
#30
† po QD

Celsentri 150mg
#30
† po BID

Despite a difference in frequency of administration (once daily vs. twice daily), DMETS has learned from post-marketing experience that the dosing frequency may not be enough to prompt practitioners as to what the product is, if both names look similar when scripted (e.g., Reminyl [dosed BID] and Amaryl [dosed QD], and Amicar [dosed every 6 to 8 hours] and Omacor [dosed QD or BID]). Thus, a written prescription for "Celsentri 300 mg po BID" can be misinterpreted as "Celontin 300 mg po BID". The differences in frequency may not be sufficient to differentiate the names because of the overlapping strength and strong orthographic similarities.

Both Celontin and Celsentri begin with "Cel", thus, the potential exists for both products to be placed side-by-side on pharmacy shelves. Products are generally stored by either tradename, generic name, or sponsor. In any of these cases, the products will be in close proximity to one another. Since both

products are made by Pfizer, the labeling looks similar (see below). Similar product appearance as illustrated below and similar storage conditions could lead to shelf selection errors. Additionally, the potential for selection errors is compounded by their overlapping strengths (150 mg and 300 mg).



If Celontin is mistakenly dispensed in place of Celsentri, a patient will experience a delay in HIV treatment, which may affect the patient's quality of life. If a patient receives Celsentri in place of Celontin, the patient will unnecessarily be exposed to an HIV drug and may experience negative side effects from the medication. Furthermore, the patient will be at an increased-risk of seizures, which may be harmful to the patient or others depending upon the situation when the patient experiences the seizure.

Due to the strong orthographic similarities, overlapping product characteristics (strength, usual dose, total daily dose, route of administration, dosage form), and similar corporate dress, DMETS reiterates its position that these products may not safely co-exist in the marketplace.

In the review of the container labels, carton and insert labeling of Celsentri, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following areas of improvement, which may minimize potential user error.

A. GENERAL COMMENT

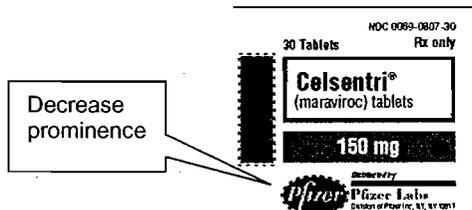
DMETS notes that Pfizer is the sponsor for both Celsentri and Celontin. The packaging for both products appears similar because the layout of the labeling is almost identical. Since Celsentri and Celontin are similar alphabetically, and they share overlapping strengths and they may be placed side-by-side on pharmacy shelves which may increase the potential for selection errors (see below). Thus, we recommend differentiating the layout of the carton and container labels of Celsentri in order to minimize shelf selection errors with Celontin.



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C. CONTAINER LABELING (150 mg and 300 mg tablets: 30 count and 60 count)

1. See General Comment.
2. De-bold the net quantity (30 tablets and 60 tablets) in order to avoid confusion with the product strength.
3. Decrease the prominence of the Sponsor's name at the bottom of the label, as it appears almost as prominent as the proprietary name.



D. CARTON LABEL (150 mg and 300 mg Hospital Unit Dose: 100 tablets)

1. See comment C2.
2. The statement "For In-institution use only" is unclear and may be confusing to healthcare professionals. We recommend revising the statement as follows: "For Hospital Use Only". This statement is more commonly known in the healthcare setting and is less confusing than for "in-institution use".

E. PACKAGE INSERT LABELING

1. Revise the first paragraph in the "Dosage and Administration" to begin with the sentence: "Celsentri must be given in combination with other antiretroviral medications" as it does in the highlighted section of the package insert. This sentence should appear first because it makes it clear that Celsentri cannot be given alone.
2. In the "How Supplied/Storage and Handling" section, the 150 mg and 300 mg tablets are described as "blue, biconvex, oval film-coated tablets". DMETS advises that the tablets should not be the same size, shape or color because this could lead to confusion between the product strengths. Therefore, we recommend revising the color and/or shape and size in order to minimize confusion between the product strengths.

F. PATIENT PACKAGE INSERT

No comment.

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/s/

Felicia Duffy
5/9/2007 02:44:41 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/9/2007 02:51:16 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/9/2007 02:58:24 PM
DRUG SAFETY OFFICE REVIEWER



NDA 22-128

INFORMATION REQUEST LETTER

Pfizer Inc
Attention: Leilani Kapili, Associate Director
50 Pequot Trail
New London, CT 06320

Dear Ms. Kapili:

Please refer to your December 20, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Celsentri® (maraviroc) tablets.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. In addition, we request further discussion of the Quality by Design aspects of this NDA. Please contact Amy Bertha, Regulatory Health Project Manager.

In reference to the Drug Substance we have the following comments and questions:

1. It is noted that screening DOEs were used as part of the support for the drug substance design space. For each DOE, provide a summary of the statistical analysis (i.e. correlation and regression coefficients, standard error, statistical significance). This question applies to the DOEs that were used in drug product development as well.
2. We concur that each batch of the starting material or maraviroc does not need to be monitored with a specific test for the potential genotoxic impurity, [REDACTED] because the combination of periodic testing at the [REDACTED] level in the starting material and the purge studies provide adequate assurance that [REDACTED] in maraviroc drug substance will remain at levels considered safe [REDACTED]. However, periodic monitoring of the starting material, inclusion in your vendor qualification program, and, when appropriate, verification of the capability of the purification processes, are important to ensure that the risk to patients remains low. Describe how you have addressed these issues at present, and how an appropriate level of monitoring for [REDACTED] in the starting material, UK-408,026, will be maintained in the future.
3. We concur that your purge studies have demonstrated that the risk of [REDACTED] carried through from the [REDACTED] mixture to maraviroc drug substance is very low. [REDACTED]. Has the potential for generating [REDACTED] during storage of [REDACTED] been evaluated, perhaps as part of a hold-time or retest plan for this intermediate?

[REDACTED]

1 Page(s) Withheld

 X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative

[REDACTED]

[REDACTED]

In reference to the Drug Product we have the following comments and questions:

8. Explain the high ranges compared to Assay for Content Uniformity in lots manufactured in March 2005. For example, for the 300 mg strength, Lot 980223/3002035 has an Assay value of [REDACTED], but the CU has a range of [REDACTED] with the Dissolution ranging from [REDACTED]. Some lots also have high Dissolution values compared to the Assay values. These types of discrepancies are not seen in lots manufactured at any other time, for example, Lot 980223/3007125 manufactured in December 2005, which has an assay value of [REDACTED]; a Content Uniformity range of [REDACTED] and Dissolution of [REDACTED].
9. At a minimum, we recommend adding the following in-process tests to Sections 3.2.P.3.4 to assure the drug product quality after the compression and coating steps:

[REDACTED]

[REDACTED]

13. Provide data on variation of blend uniformity.
No information is provided about blend uniformity

[REDACTED]

[REDACTED]

[REDACTED]

14. Clarify the commercial batch scale. It is shown in table 3.2.P.2.3-26 that for batch 980228 the size is [redacted] however in table 3.2.P.2.3-28, the scale of manufacturing for the same batch is listed as [redacted]. It has been stated earlier that [redacted] scale corresponds to [redacted].

15.

[redacted]

16. Include a specification for particle size in Section P.4.1 for both microcrystalline cellulose and dibasic calcium phosphate, anhydrous [redacted] excipients [redacted].

17. Online NIR data was presented [redacted]

18. Clarify the following:

[redacted]

c. What is the intended use of the Regulatory Process Description and the Dosage Form Monographs?

If you have any questions, call Amy Bertha, Regulatory Health Project Manager, at 301-796-1647.

Sincerely,

{See appended electronic signature page}

Elaine Morefield, Ph.D.
Director
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Elaine Morefield
3/29/2007 04:12:31 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 1, 2007
FROM: Kenny Shade, RPM
SUBJECT: Microbiology Request for Information
NDA 22-128, CELSENTRI (maraviroc)

Follow-up Dataset and Table for NDA 22128 Request - March 1, 2007

1. Please submit follow-up data (CD4 counts, tropism, viral load, AIDs defining events) on all the subjects (n=42) who failed (>400 copies/mL) with X4-using virus (see below). As soon as possible, please provide us with the timeframe for the submission of this data.

Please include the data for all "Follow-up" weeks in the dataset described below.

If more data will be collected on these subjects by March 20, we would like this latest data on the subjects who failed with X4 virus included in the safety follow-up March 20. For this class of drugs, we have requested 3-5 years of follow-up for subjects who experience virologic failure in phase 2 and 3 studies. We recommended that assessments should occur 2-3 times a year for CD4+ cell counts, viral load, viral tropism, and occurrence of AIDS-defining illnesses and death.

ID	ARM	Outcome	Week of failure	Week of Follow-up	BTRP	TRP fail	TRP at follow-up	Viral load at failure	Viral load of Follow-up	CD4 counts at failure	CD4 counts at Follow-up	AIDS defining events (Y/N)	Description of AIDS defining events

Dataset: Description of Column headings

* If AIDs defining event present at time of failure, = 0

Study	Median change in time of Follow-up from failure	% Subjects who still had X4-tropic virus at Follow-up following Failure (N)	% of Subjects who had a decrease in CD4+ Cell Counts (N)	Mean change in CD4+ Cell Counts at Time of Follow-up from Time of Failure	Median change in CD4+ Cell Counts at Time of Follow-up from Time of Failure	% of Subjects who failed with X4-tropic virus who had AIDS defining events at Follow-up	Median from : AIDS event exper. AIDS event
Study 1027							
Study 1028							
Study 1029							

Table.

Use the latest (most current) "Follow-up" sample for determination of above columns.

Treatment Failures from Study 1027 with X4 Tropic Virus at Failure (n=31)

<u>PID</u>	<u>Arm</u>	<u>Outcome</u>	<u>BTRP</u>	<u>TRP Fail</u>
A4001027 10050010	QD	VL > 400	Dual Mixed	X4
A4001027 10050038	BID	Treatment failure	R5	X4
A4001027 10070018	BID	Treatment failure	R5	X4
A4001027 10120016	QD	VL > 400	Dual Mixed	X4
A4001027 10130001	BID	Treatment failure	Dual Mixed	X4
A4001027 10190006	QD	VL > 400	Dual Mixed	X4
A4001027 10220008	QD	Treatment failure	R5	X4
A4001027 10230012	QD	VL > 400	R5	X4
A4001027 10230068	BID	Treatment failure	R5	X4
A4001027 10240019	QD	VL > 400	R5	X4
A4001027 10240024	QD	Treatment failure	R5	X4
A4001027 10240029	BID	Treatment failure	Dual Mixed	X4
A4001027 10370005	QD	Treatment failure	R5	X4
A4001027 10430022	QD	VL > 400	R5	X4
A4001027 10480025	BID	Treatment failure	Dual Mixed	X4
A4001027 10480028	QD	Treatment failure	Dual Mixed	X4
A4001027 10500012	BID	Treatment failure	R5	X4
A4001027 10520021	Placebo	Treatment failure	Dual Mixed	X4
A4001027 10530016	BID	VL > 400	R5	X4
A4001027 10670006	QD	VL > 400	R5	X4
A4001027 10670008	QD	Treatment failure	R5	X4
A4001027 10680006	BID	Treatment failure	R5	X4

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A4001027 10720009	BID	DC and VL > 400	Dual Mixed	X4
A4001027 10740001	QD	VL > 400	R5	X4
A4001027 10990015	BID	Treatment failure	R5	X4
A4001027 11010002	BID	Treatment failure	Dual Mixed	X4
A4001027 11090001	QD	Treatment failure	R5	X4
A4001027 11110011	QD	Treatment failure	Dual Mixed	X4
A4001027 11300004	QD	DC VL > 400	R5	X4
A4001027 11480001	QD	Treatment failure	R5	X4
A4001027 11480004	BID	VL > 400	R5	X4

Treatment Failures from Study 1028 with X4 Tropic Virus at Failure (n=11)

A4001028 10020007	BID	Treatment failure	R5	X4
A4001028 10440002	QD	DC VL > 400	R5	X4
A4001028 10440004	BID	Treatment failure	R5	X4
A4001028 10510008	BID	Treatment failure	Dual Mixed	X4
A4001028 10880018	QD	VL > 400	Dual Mixed	X4
A4001028 10890001	BID	Treatment failure	Dual Mixed	X4
A4001028 10890013	BID	>400	R5	X4
A4001028 10920002	Placebo	DC VL > 400	R5	X4
A4001028 11130002	QD	Treatment failure	R5	X4
A4001028 11540001	QD	VL > 400	R5	X4
A4001028 11580007	QD	Treatment failure	R5	X4

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/s/

Kenny Shade
3/2/2007 12:14:56 PM
CSO



Food and Drug Administration
Division of Antiviral Products
Office of Antimicrobial Products
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 22-128
Drug: CELSENTRI® (maraviroc)
Date: March 1, 2007
To: Leilani V. Kapili, MA
Sponsor: Pfizer Inc.
From: Kenny Shade, JD, BSN
Through: Pravin Jadhav, PhD
Christine Garnett, PharmD
Scott Proestel, MD
Concur: Katherine Laessig, MD, Medical Officer Team Leader
Subject: Cardio-Renal Consult team clarification comments

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) submitted December 20, 2006. The following clarifications are being sent in response to an email request sent by the sponsor on February 27, 2007 to the QT consult team. The sponsor's questions are in bold print with the Agency's response in italic print.

Review Team Comments

1. **Our current datasets include the time-matched change in QTcI using the placebo run-in day from Period 3 as the baseline. The dataset request asked for the change from placebo of these changes i.e. time-matched change in QTcI for maraviroc minus the corresponding time-matched change for placebo, we didn't calculate this as the run-in period was a placebo run-in – Can you clarify that this is required (labelled as ddQTc on the dataset request).**

We do recognize the use of placebo during the run-in period. We are interested in analyses using Day 1 for all study subjects (use of randomized study periods). On that end, the current ddQTc will be equivalent to using placebo data as a reference for each subject (as the run-in day will cancel out for moxifloxacin and maraviroc). Also, we do understand that the ddQTc for placebo will be zero for all subjects. Please submit the data as indicated.

2. **The request asked that any data not collected during the study should be coded on the dataset as missing, 3 subjects were withdrawn during the study and we propose to exclude records for these subjects after the point of withdrawal rather than include missing records for each planned visit after withdrawal.**

You can exclude 3 subjects data post withdrawal from the study. Please mark them as dropouts using an informative variable. For subjects who completed the study, if the planned sample(s) is missing, please indicate so.

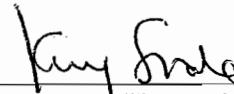
3. **Plasma concentrations were not measured for moxifloxacin therefore our current datasets for exposure-response analysis do not include the moxifloxacin QT data as there are no corresponding concentration data, can you confirm that this is not required.**

Please indicate moxifloxacin concentrations as missing using ‘.’

4. **Two time variables were requested (TIME and SAMPLE) both of these seem to relate to the planned time, we propose to include the planned time and the actual time relative to dosing in the dataset**

Please submit planned time (SAMPLE) and actual time relative to dosing (TIME)

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.



Kenny Shade, JD, BSN
Regulatory Project Manager
Division of Antiviral Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

Kenny Shade
3/1/2007 01:01:04 PM
CSO

Kathrine Laessig
3/1/2007 01:37:11 PM
MEDICAL OFFICER



MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 26, 2007
TIME: 2:30 pm
LOCATION: WO Conference Room 6326
APPLICATION: NDA 22-128
DRUG NAME: CELSENTRI (Maraviroc)
SPONSOR: Pfizer, Incorporated
TYPE OF MEETING: Information Request Telecon

FDA Participants:

Scott Proestel, M.D., Medical Officer
Victoria Tyson-Medlock, Regulatory Project Manager

Pfizer Incorporated Participants:

Leilani Kapilli, MA, Director, Worldwide Regulatory Affairs and Quality Assurance

DISCUSSION:

This teleconference was held to get clarification and to request additional information on the following issues:

- Dr. Proestel asked the sponsor to confirm that there were a total of 601 subjects randomized in study 1027 and 585 subjects who received at least one dose of study agent.
- Dr. Proestel asked the sponsor about the status of the response to the request for baseline weights for all subjects in studies 1027 and 1028 that was made during the February 23, 2007, teleconference. The sponsor will contact the Division on February 27, 2007, to provide the date that this information will be submitted. The Division asked the sponsor to submit this information in a table with all baseline weights that includes a column with the visit that the weights were taken if it was not taken at baseline.
- Dr. Proestel asked the sponsor for clarification on the interpretation of the following codes that are being used for reporting adverse events:

PRE- pretreatment;
BID-twice a day regimen;
QID-this is a typographical error and is actually QD-once a day;
OFF-TRT- off treatment not on double-blind or open label;

OL-open label, BID;
PLA-placebo;
ISOD-in study off drug; and
POST- study drug is discontinued but subject remains in the study

The sponsor confirmed the above definitions. Dr. Proestel asked the sponsor to clarify the difference between OFF TRT, ISOD, and POST. The sponsor stated that she would provide a clarification on the differences between these terms as soon as possible.

A follow-up teleconference will be scheduled to discuss this information. However, the sponsor is not sure when this call will take place since some of the personnel assigned to this NDA are at CROI this week.

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/s/

Victoria TysonMedlock
2/28/2007 03:21:31 PM
CSO

Executive CAC

Date of Meeting: February 20, 2007

Committee: David Jacobson-Kram, Ph.D., OND-IO, Chair
Joseph Contrera, Ph.D., OPS, Member
Chuck Resnick, Ph.D., DCRP, Alternate Member
James G. Farrelly, Ph.D., DAVP, Team Leader
Pritam (Pete) Verma, Ph.D., DAVP, Presenting Reviewer

Author of Minutes: Pete Verma, Ph.D.

The following brief summary reflects the Committee discussion and its recommendations. Detailed study information can be found in the Dr. Verma's review.

NDA #: 22-128

Drug: Maraviroc (UK-427,857) is an inhibitor of HIV-1 entry. This new chemical entity acts by selectively binding to the human chemokine receptor CCR5 and inhibiting the interaction of the envelope glycoprotein (gp120) from CCR5-tropic HIV-1 strains with CCR5. Binding of gp120 to CCR5 is an essential step in the HIV-1 entry process for CCR5-tropic strains. Targeting a human protein in order to prevent viral entry is a new approach to HIV-1 therapy.

Sponsor: Pfizer Global Research & Development
50 Pequot Ave
New London, CT 06320

Rat Carcinogenicity Study: The oncogenicity potential of maraviroc was investigated in Sprague-Dawley rats with oral gavage dosages of 50, 100, 500 or 900 mg/kg/day in comparison with vehicle controls for a period of 104 weeks in males and 96 weeks in females. (All female groups were terminated early when survival in the female control group dropped to 33% (20 of 60 rats surviving to 96 weeks).

Although there were statistically significant positive trends ($p < 0.05$) for several tumor types, only the incidence of follicular cell adenoma of the male thyroid also achieved statistical significance in a pairwise comparison of the high dose with the vehicle control ($p < 0.05$). A clearly drug and dose-related increase in thyroid follicular cell hyperplasia and hypertrophy was observed at doses of 100 mg/kg/day and above in males and 500 mg/kg/day in females. The tumor incidence was within the historical control range for this strain of rat and no follicular cell carcinomas were found in the thyroid gland. Also noteworthy was a significant positive trend for the incidence of cholangiocarcinoma of the male liver ($p < 0.05$). Although observed in only 2 high dose males and not significant in a pairwise comparison with the vehicle control, available data appears to indicate that cholangiocarcinoma is a rare tumor in the Sprague-Dawley rat (< one rat in 1800).

Executive CAC Recommendations and Conclusions:

The committee found the carcinogenicity study in the rat to be acceptable and noted that the protocol had been approved by the Exec CAC. The Committee found the evidence for drug-related neoplasia to be equivocal at best, noting the absence of any trend analysis or pairwise comparison p value <0.01 for any of the increases in tumor incidence identified by the CDER statistician, an especially important observation in the case of the thyroid follicular cell adenoma, a common tumor type in the S-D rat. As for the cholangiocarcinomas, apparently rare in the S-D rat, the committee noted the absence of a statistically significant difference between the incidences observed in the high dose and vehicle control groups and considered the finding less than sufficient to clearly implicate the drug.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc: \
/Division File, DAVP
/JFarrelly, DAVP
/PVerma, DAVP
/KShade, DAVP
/ASeifried, OND IO

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/s/

David Jacobson-Kram
2/27/2007 10:39:58 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,229

Pfizer Inc.
Attention: Leilani Kapili, MA
50 Pequot Avenue
New London, CT 06320

Dear Ms. Kapili:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Maraviroc (UK-427,857) oral tablet.

We also refer to the meeting between representatives of your firm and the FDA on November 28, 2006. The purpose of the meeting was to discuss the results of studies A4001027 and A4001028 and the adequacy of the proposed dossier.

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 Kenny Shade, Regulatory Project Manager, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant
Division Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 28, 2006
TIME: 10 am
LOCATION: 10903 New Hampshire Avenue, Silver Spring, MD
APPLICATION: IND: 65,229
DRUG NAME: Maraviroc (UK-427-857)
TYPE OF MEETING: Pre-NDA

FDA ATTENDEES: (Title and Office/Division)

Jeffrey Murray, Acting Deputy Director Office of Antimicrobial Products (OAP)
Debra Birnkrant, Director, Division of Antiviral Products
Katherine Laessig, Acting Deputy Director, Division of Antiviral Products
James Farrelly, Pharmacology/Toxicology Team Leader, Associate Director
Scott Proestel, Medical Officer
Kellie Reynolds, Deputy Director, Division of Clinical Pharmacology IV
Jenny H. Zheng, Clinical Pharmacology Reviewer
Julian O'Rear, Microbiology Team Leader
Lisa Naeger, Microbiology Reviewer
Guoxing Soon, Biometrics Team Leader
Susan Zhou, Biometrics Reviewer
Stephen Miller, Chemistry
Virginia Behr, Chief, Project Management Staff
Kenny Shade, Regulatory Health Project Manager
Kendall Marcus, Medical Officer Team Leader
Kimberly Struble, Medical Officer Team Leader
John O'Malley, Information Technology
Diane Wysowski, Epidemiologist
Paula Gish, Safety Evaluator, Office of Safety Evaluation
Melissa Truffa, Safety Evaluator Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

Leilani Kapili, Director, Regulatory Lead
Howard Mayer, Executive Director, Global Clinical Leader
John Sullivan, Clinical Statistics Lead
Lynn McFadyen, Pharmacometrics
Sam Abel, Clinical Pharmacology Leader
Steve Felstead, Development Team Leader
James Goodrich, Lead Clinician
Mary McHale, Risk Management Lead
Sarah Nuttall, RAD
Elna van der Ryst, EU Clinical Leader
Mike Westby, Virology Lead

BACKGROUND:

This meeting was held at the request of the sponsor Pfizer Inc. Pfizer submitted the background package on October 31, 2006. After the Division's internal meeting a fax was sent to Pfizer on November 21, 2006 requesting additional analyses and comments on the structure of the clinical and microbiology sections of the NDA.

MEETING OBJECTIVES:

- 1) To review the results of studies A4001027 and A4001028
- 2) To discuss the results of the virology and population pharmacokinetic studies
- 3) To discuss the adequacy of the proposed dossier

DISCUSSION POINTS/DECISIONS REACHED:

- Following introductions, Ms. Kapili described the agenda for the meeting. The Pfizer team planned to give an overview of the results of two registrational trials, A4001027 and A4001028, a summary of the structure and content of the eCTD submission, the expanded access program, and the post-NDA submissions, including the proposal for the 4-month safety update.
- Dr. Mayer gave an overview of the two studies, including more recent analyses which were not available in the meeting package, to share the subgroup analyses when the BID vs QD dosing regimens were compared. Dr. McFadyen then described the preliminary exposure response analyses.
- Dr. Proestel specified that the placebo group must be clear in the tables.
- Dr. Proestel asked whether it was possible to determine in the safety dataset what therapy the patient was taking at the start of each AE listed. He specified the need to be able to determine whether any given patient had ever received maraviroc at any time prior to an AE.
Pfizer indicated they would follow-up if this was possible to determine with the datasets prepared.
- Dr. Proestel asked whether or not either of the two placebo deaths received maraviroc and Pfizer's response was no.
- Dr. Proestel requested narratives for all Category C events, including cases of herpes simplex and esophageal candidiasis.
- Because of a 6-month review clock a 3-month safety update was requested by the Division.
- Dr. Proestel commented that the data from studies 1027 and 1028 would need to be reviewed before the Division could agree to the proposed design and revised inclusion/exclusion criteria for the Expanded Access Program (EAP). When asked to comment on the recommended 300 mg BID dose, Dr. Proestel indicated he would prefer waiting until he completed his review of studies 1027 and 1028. Dr. Proestel noted that we don't

see any incremental problems with BID dosing but that no definitive answer could be given at this time. Dr. Murray responded that it is preferable to select a dose that can cover patients with higher viral loads. Dr. Murray indicated that the 300 mg BID dose appears appropriate from an efficacy viewpoint.

- Dr. Laessig asked about the patients co-infected with hepatitis B or C virus. Dr. Mayer responded that approximately 6% of the patients were co-infected and analyses of this subgroup will be included in the SCS.
- Dr. Zheng noted that the PK data indicated that many of the subjects in the BID group did not take the second dose. Dr. McFadyen explained that many of the patients did not take the morning dose on the day they visited the clinic. The time of the last dose is recorded in the database.
- Dr. Murray inquired what dose of saquinavir/ritonavir was used. Pfizer responded that typically, the boosted dose was 1000 saquinavir/100 ritonavir BID.
- Dr. Soon requested that additional efficacy analysis for studies 1027 and 1028 be submitted past 24 weeks. Pfizer responded that this data has not been analyzed yet. Dr. Soon asked that this data be provided to the Division.
- Dr. Naeger asked if Pfizer planned on submitting a test dataset before the NDA submission. Pfizer indicated that they may not be able to provide datasets before the NDA was submitted given the timelines, but that the data definitions would be provided. Dr. Naeger agreed this would allow her to see if all the columns needed were included. It was agreed that a virology teleconference would be arranged to discuss the appropriate format for the submission of this information.
- Dr. O'Rear suggested that the tropism be addressed separately in the label. It was agreed that tropism and resistance would be addressed separately in the label.
- Dr. Birnkrant requested the following actions:
 - A rapid response/turn-around to FDA queries during the review period to enable efficient review
 - Additional efforts to locate any patients who were lost to follow up. She noted that knowing the outcomes for all patients has been a key point for past submissions. These patients can be included in the three-month safety update.
 - Regarding the lymphoma issue, Dr. Birnkrant asked if Pfizer had considered a registry since it will be important to be able to follow patients long-term. It was stressed that the question of lymphomas and malignancies was still "out there" and would likely be a topic for discussion at the Advisory Committee meeting. Pfizer responded that they planned on following all patients for five years.
- There were no additional comments on the proposed eCTD format, as summarized in the premeeting package. It was confirmed that the highlights section of the USPI would not be coded for the initial submission but a fully compliant label in SPL format would be available prior to the labeling negotiations.

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/s/

Debra Birnkrant
2/13/2007 11:34:36 AM
IND 65,229



FILING COMMUNICATION

NDA 22-128

Pfizer Inc.
Attention: Leilani V. Kapili
50 Pequot Avenue
New London, CT 06320

Dear Ms. Kapili:

Please refer to your December 20, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CELSENTRI® (maraviroc) oral tablets.

We also refer to your submission dated November 21, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 18, 2007, in accordance with 21 CFR 314.101(a). This NDA has been granted a priority review and the user fee goal date will be June 20, 2007.

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Kenny Shade, Regulatory Project Manager, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Debra Birnkrant
2/9/2007 12:18:20 PM
NDA 22-128

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): DDRE/ Office of Surveillance and Epidemiology		FROM: Elizabeth Thompson, Safety RPM 301-796-0824		
DATE 2-6-07	IND NO.	NDA NO. 22-128	TYPE OF DOCUMENT New NDA (Risk Management Plan)	DATE OF DOCUMENT December 20, 2006
NAME OF DRUG Celsentri		PRIORITY CONSIDERATION ASAP (This will go to Advisory Committee on April 24, 2007)	CLASSIFICATION OF DRUG Antiviral	DESIRED COMPLETION DATE Before Advisory Committee mtg (4/24/07)
NAME OF FIRM: Pfizer, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY				
<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT				
<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This is a new NDA with a Risk Management Plan that the Division of Antiviral Products would like OSE to review. The PDUFA date is June 20, 2007 and this will go to Advisory Committee on April 24, 2007. Please contact Elizabeth Thompson if you have any questions regarding this NDA. Please note that this NDA submission is completely electronic and in eCTD format. The RMP is located on the EDR.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL (DFS) <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Elizabeth Thompson
2/6/2007 02:51:42 PM



Food and Drug Administration
Division of Antiviral Products
Office of Antimicrobial Products
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: 22-128
Drug: CELSENTRI® (maraviroc)
Date: February 1, 2007
To: Leilani Kapili
Sponsor: Pfizer Inc.
From: Kenny Shade, JD, BSN
Through: Scott Proestel, MD
Susan Zhou, PhD
Pravin Jadhav, PhD
Concur: Katherine Laessig, MD
Guoxing Soon, PhD
Jogarao Gobburu, PhD
Subject: Review Team Comments

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-128 for CELSENTRI® (maraviroc) submitted December 19, 2006.

Review Team Comments

In the pre-NDA meeting on November 28, 2006, the statistical reviewer requested the SAS XPT files be submitted to the FDA electronic document room (EDR) with SAS programs. To date we have not received any SAS programs. Please submit key SAS programs with appropriate instructions for Studies A4001027, A4001028 and A4001029 as soon as possible. In addition, we have the following additional questions and request:

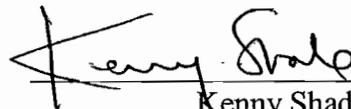
1. It is unclear how the Full Analysis Sets (FAS) and Per Protocol (PP) datasets were created. Please submit the key SAS programs to summarize subjects' status in screening, inclusion/exclusion, randomization, and treatment, so that the indicators such as FAS, PP, etc., in datasets "anlpop.xpt" can be clearly understood.
 - Some datasets for Studies A4001027 and A4001028 had discrepancies in their variables. For example, the variable "Randtst" is in "anlpop.xpt" under A4001027 but not in A4001028. Please comment.

March 14, 2006

2. Please submit SAS programs for creating the efficacy datasets such as vir27.xpt, vir28.xpt and vir29.xpt under the subdirectory of /datasets/virology.

- It appears that the number of randomized subjects in your report are different from the numbers of distinguished PID in vir**.xpt. Please clarify

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.



Kenny Shade, JD, BSN
Regulatory Project Manager
Division of Antiviral Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

Kenny Shade
2/1/2007 12:38:40 PM
CSO

Kathrine Laessig
2/9/2007 03:59:58 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22, RM 4447		FROM: Kenny Shade, Regulatory Health Project Manager Division of Antiviral Products		
DATE January 25, 2007	IND NO.	NDA NO. 22-128	TYPE OF DOCUMENT Trade Name Review Request	DATE OF DOCUMENT December 20, 2006
NAME OF DRUG Celsentri		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG 7030140	DESIRED COMPLETION DATE May 1, 2007
NAME OF FIRM: Pfizer Global Research & Development				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This name was previously reviewed (IND 65,229) by your division prior to NDA submission. The NDA has been granted priority (6 month) review with Advisory Committee meeting April 24, 2007. Please note the NDA was submitted electronically and all submission can be located in EDR (electronic document room).				
PDUFA DATE: June 20, 2007 ATTACHMENTS: Draft Package Insert, Container and Carton Labels CC: Archival IND/NDA IND: 65,229/NDA 22-128 HFD-530/Division File HFD-530/RPM HFD-530/Reviewers and Team Leaders				
NAME AND PHONE NUMBER OF REQUESTER Kenny Shade 301-796-0807		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Kenny Shade
1/26/2007 07:54:38 AM

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 25, 2007

TO: Associate Director
International Operations Drug Group
Division of Field Investigations (HFC-130)

Director, Investigations Branch
New Jersey District Office
Waterview Corp Ctr
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

From: C.T. Viswanathan, Ph.D. CTV 1/26/07
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

Through: Gary Della'Zanna, D.O., M.Sc. [Signature]
Director
Division of Scientific Investigations (HFD-45)

SUBJECT: FY 2007, High Priority CDER 'User Fee' NDA, Pre-Approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001, PAC 48001E

RE: NDA 22-128
DRUG: CELSENTRI (maraviroc)
SPONSOR: Pfizer Global Research and Development
Address: 50 Piquot Avenue
New London, CT 06320

This memo requests that you arrange for an inspection of the clinical and analytical portions of a bioequivalence study of antiretroviral drug product, sponsored by Pfizer. Due to the user fee due date, we request that these inspections be completed by May 04, 2007.

Study# A4001040: "An open, randomised, 2 way crossover study to confirm bioequivalence of the maraviroc research

tablet (2 x 150 mg) and the commercial tablet (300 mg)".

Clinical Site: Pfizer Clinical Research Unit
Block 7, Level 7, Singapore General,
Hospital Outram Road,
Singapore 169608

Clinical Investigator: Anthony Rebuck, M.D..
TEL: 65-6325 5501
FAX: 65-6325 4976

Please check the batch numbers of both the test and the reference drug formulations used in the study with descriptions in the documents submitted to the Agency. Samples of both the test and reference drug formulations should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening.

Please have the records of all study subjects audited. The subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, pharmacokinetic blood sample collection and processing, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR.

Analytical Site: _____

Analytical Investigator: _____

Methodology: LC-MS/MS

_____ analyzed the plasma samples collected in Study A4001040 for maraviroc concentrations.

All pertinent items related to the analytical methods should be examined and the sponsor's data should be audited. The

Page 3 - BIMO Assignment, NDA 22-128, CELSENTRI (maraviroc 300 mg) Tablets

chromatograms provided in the NDA submission should be compared with the original documents at the firm. The method validations and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following the identification of the investigator, background material will be forwarded directly. **A scientist from the GLP and Bioequivalence Investigations Branch Team in DSI with specialized knowledge will participate in the inspection.**

Headquarters Contact Person: Jagan Mohan R. Parepally, Ph.D.
(301) 594-2042

cc:
DSI/RF
DSI/GLPBB/Parepally/Himaya/CF
OND/DAVP/Shade/Zheng
HFR-CE300/Kelahan (BIMO; please fax)
Draft: JP 01/25/07
Edit: MKY 01/26/07
DSI: 5745; O:\BE\assigns\bio22128.doc
FACTS: 801718

NJ FEI 3004059012

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NDA 22-128

NDA ACKNOWLEDGMENT

Pfizer Inc.
Attention: Leilani V. Kapili
50 Pequot Avenue
New London, CT 06320

Dear Ms. Kapili:

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

Name of Drug Product: CELSENTRI® (maraviroc) Oral

Review Priority Classification: Priority

Date of Application: December 19, 2006

Date of Receipt: December 20, 2006

Our Reference Number: NDA 22-128

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, 2007, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be June 20, 2007.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA 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 Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Kenny Shade, Regulatory Project Manager, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Virginia Behr
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Virginia Behr
1/23/2007 01:49:33 PM

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/s/

Kenny Shade
1/23/2007 12:34:25 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,229

Leilani V. Kapali, MA
Associate Director, Worldwide Regulatory Affairs
50 Pequot Avenue
New London, CT 06320

Dear Ms. Kapali:

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

We also refer to our April 29, 2005 letter granting fast track designation for maraviroc your November 8, 2006, request for rolling review submission of sections of the New Drug Application (NDA) for this product.

We have reviewed your request and have concluded that the proposed plan for rolling review submission of sections of the NDA is acceptable.

If you pursue a clinical development program that does not support use of Maraviroc for treatment of HIV-1 infection, the application will not be reviewed under the fast track drug development program and submission of sections of the NDA will not be permitted under this program.

If you have any questions, call Kenny Shade, Regulatory Project Manager, at 301-796-0807.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Debra Birnkrant
12/18/2006 11:36:08 AM
IND 65,229



WRITTEN REQUEST

IND 65,229

Pfizer Inc.
Attention: Leilani V. Kapili, MA
50 Pequot Avenue
New London, CT 06320

Dear Ms. Kapili:

To obtain needed pediatric information on maraviroc (UK-427,857), the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Type of studies:

1. A multiple-dose pharmacokinetic, safety and activity study of maraviroc in combination with other antiretroviral agents in HIV-infected pediatric patients
2. A multiple-dose pharmacokinetic and safety study of maraviroc in HIV-exposed neonates (born to HIV-infected mothers)

The objective of these studies will be to determine the pharmacokinetic and safety profile of maraviroc across the age range studied, identify an appropriate dose for use in HIV-infected pediatric patients and exposed neonates, and evaluate the activity of this dose (or doses) in treatment and/or prophylaxis.

Indication to be studied:

Treatment of HIV infection in pediatric patients and/or prophylaxis of HIV infection in exposed neonates.

Age group in which study (ies) will be performed:

HIV-infected pediatric patients from 1 month to adolescence and HIV-exposed neonates (born to HIV-infected mothers).

Drug Information

Dosage form: age appropriate-formulation

Route of administration: oral

Regimen: to be determined by development program

Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and

testing a new dosage form for which you will seek approval for commercial marketing. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

Development of a commercially-marketable formulation is preferable. If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and if necessary, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug specific safety concerns:

Based on available toxicity information with your product, please provide specific safety parameters that your pediatric program will address including but not limited to:

1. Hepatotoxicity
2. Infection
3. Malignancy
4. Tropism switching

Safety of maraviroc must be studied in an adequate number of pediatric patients or neonates to characterize adverse events across the age range. A minimum of 100 patients with at least 24 weeks safety data is required.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients and descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates (born to HIV-infected mothers).

A minimum number of pediatric patients (as stated below) must complete the pharmacokinetic studies conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

Birth to < 6 weeks: 8

6 weeks to < 6 months: 6

6 months to < 2 years: 6

2 years to < 6 years: 12

6 years to < 12 years: 8

12 years to 18 years: 6

Studies must include an adequate number of patients to characterize pharmacokinetics and select a therapeutic dose for the age ranges studied, taking into account inter-subject and intra-subject variability. The number of patients must be approximately evenly distributed across the age range studied.

Study Endpoints:

Pharmacokinetics

Parameters such as C_{max} , C_{min} , T_{max} , $t_{1/2}$, AUC and apparent oral clearance.

Safety and tolerability

HIV-infected pediatric patients should be followed for safety for a minimum of 24 weeks at the recommended dose. HIV-exposed neonates (born to HIV-infected mothers) should have safety assessments, on or off treatment (as appropriate), for a minimum of 24 weeks after start of therapy. In addition, please also submit plans for long-term safety monitoring in HIV-exposed neonates and HIV-infected pediatric patients who have received maraviroc.

Activity

Assessment of changes in plasma HIV RNA levels and in CD4 cell counts.

Resistance

Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving maraviroc, particularly from those who experience loss of virologic response.

Labeling that may result from the study (ies):

Information regarding dosing, safety and activity in HIV-infected pediatric population and information regarding dosing and safety in HIV-exposed neonates (born to HIV-infected mothers).

Format of reports to be submitted:

You must submit full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of the study (ies):

Reports of the above studies must be submitted to the Agency on or before December 30, 2011. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. The type of response to the Written Request (complete or partial);
2. The status of the supplement (withdrawn after the supplement has been filed or pending);
3. The action taken (i.e. approval, approvable, not approvable); or
4. The exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at <http://www.fda.gov/cder/pediatric/Summaryreview.htm> and publish in the Federal Register a notification of availability.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR**

PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data bank (<http://clinicaltrials.gov> & <http://prsinfo.clinicaltrials.gov/>). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site <http://prsinfo.clinicaltrials.gov/>.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, contact [insert project manager name and title], at 301-796-0807.

Sincerely yours,

{See appended electronic signature page}

Edward Cox, MD
Acting Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Jeffrey Murray
11/28/2006 02:08:25 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND: 65,229

Pfizer Inc.
Attention: Leilani V. Kapili, MA
50 Pequot Ave.
New London, CT 06320

Dear Ms. Kapili:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal, Food, Drug, and Cosmetic Act for Maraviroc (UK-427,857).

We also refer to your September 13, 2006, correspondence, received September 14, 2006, requesting a Pre-NDA meeting to discuss the results from studies A4001027 and A4001028, the adequacy of the proposed dossier and the results of the virology and population pharmacokinetic studies.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: Tuesday, November 28, 2006

Time: 10:00am to 12:00pm EST

Location: 10903 New Hampshire Ave. Bldg 22, Room 1419, Silver Spring, MD 20903

CDER participants: Kenny Shade, Regulatory Project Manager
Edward Cox, Acting Office Director
Jeffrey Murray, Acting Office Deputy Director
Debra Birnkrant, Division Director
Katherine Laessig, Acting Deputy Division Director
Scott Proestel, Medical Officer
Julian O'Rear, Microbiology Team Leader
Lisa Naeger, Microbiology Reviewer
James Farrelly, Pharmacology/Toxicology Team Leader
Pritam Verma, Pharmacology/Toxicology Reviewer
Guoxing Soon, Biometric Team Leader
Susan Zhou, Biometric Reviewer
Norman Schmuff, Chemistry Supervisor
Stephen Miller, Chemistry Team Leader
John Lazor, Clinical Pharmacology Supervisor
Kellie Reynolds, Clinical Pharmacology Team Leader
Jenny H. Zheng, Clinical Pharmacology Reviewer

IND: 65,229

Page 2

Virginia Behr, Chief, Project Management Staff
Kenneth Edmunds, IT Systems Analysis

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to meat Kenny.Shade@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance.

Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Kenny Shade, ext. 6-0807; the division secretary, ext. 6-1500

Provide the background information for this meeting (three copies to the IND and twenty desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by October 28, 2006, we may cancel or reschedule the meeting.

If you have any questions, call Kenny Shade, Regulatory Project Manager, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Kenny Shade
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Kenny Shade
9/28/2006 09:57:48 AM

REQUEST FOR CONSULTATION

TO (Division/Office):
**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
WO22, RM 4447**

FROM: **Kenny Shade, Regulatory Health Project Manager
Division of Antiviral Products/301-796-0807**

DATE June 12, 2006	IND NO. 65,229	NDA NO.	TYPE OF DOCUMENT General Correspondence: Trade Name Review Request	DATE OF DOCUMENT June 6, 2006
NAME OF DRUG Maraviroc (UK-427,857)		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG 7030140	DESIRED COMPLETION DATE September 12, 2006

NAME OF FIRM: **Pfizer Global Research & Development**

REASON FOR REQUEST

I. GENERAL

- | | | |
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| <input type="checkbox"/> NEW PROTOCOL
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<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
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<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
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<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
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II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
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III. BIOPHARMACEUTICS

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<input type="checkbox"/> BIOAVAILABILITY STUDIES
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<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

IV. DRUG EXPERIENCE

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| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
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V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS:

PDUFA DATE:
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
 CC: Archival IND/NDA 43,325
 HFD-530/Division File
 HFD-530/RPM
 HFD-530/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER Kenny shade, 301-796-0807	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
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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.**

/s/

Kenny Shade

6/12/2006 09:24:34 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,229

Pfizer Global Research and Development
Attention: Leilani K. V. Kapili, MA
Associate Director
Worldwide Regulatory Strategy and Quality Assurance
50 Pequot Avenue
New London, CT 06320

Dear Ms. Kapili

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for UK-427,857 (CCR5 antagonist).

We also refer to the meeting between representatives of your firm and the FDA on October 7, 2004. The purpose of the meeting was to discuss end-of-phase-II (EIO2) chemistry, manufacturing, and Controls (CMC) and bioequivalence (BE) issues.

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 Marsha Holloman, Regulatory Health Project Manager, at (301) 827-2335.

Sincerely,

(See appended electronic signature page)

Marsha S. Holloman, BS Pharm, JD
Regulatory Health Project Manager
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 7, 2004
TIME: 9:30 AM
LOCATION: 9201 Corporate Blvd, Conference Room S400
TYPE OF MEETING: End of Phase 2 (EOP2)

APPLICATION: IND 65,229
DRUG NAME: UK-427,857
SPONSOR: Pfizer Global research and Development

MEETING CHAIR: Stephen P. Miller, PhD
Chemistry, Manufacturing and Controls (CMC) Team Leader

MEETING RECORDER: Marsha S. Holloman, BS Pharm, JD
Regulatory Health Project Manager

FDA ATTENDEES:

Vikram Arya, PhD, Bioequivalence Reviewer, Division of Antiviral Drug Products (DAVDP)
Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, DAVDP
Katherine A. Laessig, MD, Medical Team Leader, DAVDP
David Linn, PhD, Lead Chemist, Division of New Drug Chemistry II
Stephen P. Miller, PhD, CMC Team Leader

PFIZER ATTENDEES:

Leilani Kapili, MS, Global Regulatory Leader
Ron Ogilvie, PhD, Regulatory CMC
Stephen Robinson, PhD, Pharmaceutical Sciences Team Leader
Susan Taylor, Pharmaceutical Research and Development

BACKGROUND

Reference is made to IND 65,299 for UK-427-857 (CCR5 antagonist) dated May 6, 2003. Also, reference is made to SN-029 dated May 5, 2004, requesting an EOP2 CMC meeting. Additionally, reference is made to SN-031 dated May 17, 2004, containing CMC amendments to the original IND protocol. Also, reference is made to SN-033 dated June 3, 2004, containing the EOP2 CMC Meeting Package. Additionally, reference is made to a DAVDP facsimile sent September 29, 2004 containing CMC review comments regarding SN-033. Finally, reference is made to SN-053 dated October 1, 2004, containing the updated CMC EOP2 Meeting Package and copies of Pfizer's slide presentation.

EXECUTIVE SUMMARY

The following agreements were reached during the meeting:

- UK-453,464 and UK-408,026 are appropriate starting materials given the information and change control strategy provided.

CDER Comment: Based upon information on synthesis (N-031 and Response 10 in N-053), carry-over of impurities (N-053), and manufacturing safety issues (N-053).

- The proposed control limit ~~_____~~ for unspecified impurities in starting materials was agreed.
CDER Comment: Specification for starting material UK-453,464 will include a chiral test as recommended in CDER fax (Sept 29, 2004); acceptance criteria to be determined (N-053).
- An initial filing with 9-month drug product stability data plus supporting data from development batches, will be acceptable for standard or priority review. Submission of the 12-month stability data within 90 days of the filing will not be considered a major amendment. Should clinical studies run ahead of current timelines, the Division said discussion with the clinical reviewers would be needed to consider a filing with less than 9 months of stability data.
- The proposed drug substance specification strategy for particle size, polymorphism and microbiological examination was endorsed.
- The proposed drug substance stability program was endorsed, including evaluation of one drug substance lot (out of three) isolated ~~_____~~.
CDER Comment: As described in N-053 (page 1).
- The use of in vitro dissolution methodology to demonstrate the equivalence of the clinical and commercial tablet formulations was discussed. In considering minor changes between the clinical and commercial drug products, the Agency advised pursuing in vitro evaluation initially with suitable (and ideally) discriminatory methodology. FDA invited the team to return and discuss the need for a BE study once further data are available.
- The proposed drug product specification strategy was endorsed.

Additional CDER Summary Statement: Agreement was reached on the plans for registration batches (Response 9 in N-053).

Pfizer agreed to provide the following data at a suitable juncture:

- A summary of dissolution studies to date and our approach for finalizing the dissolution methodology.
- Dr. Miller expressed an interest in receiving further information on the use of Moisture Vapor Transmission Rate (MVTR) to establish bracketing in the design of the drug product stability program.

CDER Comment: See discussion below and Responses 7 and 8 (N-053) for the full context.

FULL MINUTES OF OCTOBER 7, 2004 MEETING

After the introductions, Dr. Miller thanked the team for providing responses to the FDA comments quickly, which enabled the reviewers to review the additional information before this meeting [FDA comments were received by the team on September 29 and responses were sent by hard copy and e-mail to FDA on October 1; submitted as N-053]. Dr. Ogilvie thanked FDA for the helpful comments and said it was hoped the responses would help facilitate the meeting.

Ms. Kapili said it was planned for Dr. Ogilvie to present the slides included in the premeeting package (submitted June 3, 2004) and that the team would also address any points from the responses that may need further clarification. Dr. Miller agreed that this would be a suitable way to proceed. Dr. Ogilvie said he would tailor his presentation to highlight the issues raised in the Division's comments.

Choice of Starting Materials and Control Strategy

After a brief overview of the compound, Dr. Ogilvie presented the synthesis and the rationale for the choice of starting materials for UK-427,857:

UK-427,857 will be manufactured commercially at Pfizer's Ringaskiddy plant in several steps from the starting materials. The isolated product from each step is _____ . The process is a convergent synthesis from commercially available starting materials that are structurally dissimilar from drug substance, which should enable impurity purging. The two starting materials are ahead of the final intermediate in BACPAC terms.

The selected starting materials (UK-453,464 and UK-408,026) are structurally complex and therefore, development is based on understanding the routes of synthesis to support development of appropriate analytical methodology. A change management agreement with the suppliers will be managed by Pfizer to ensure that the methodology remains appropriate. This will allow Pfizer and in turn, the Agency, to be aware of any significant changes. Dr. Ogilvie stated that this should not be taken to mean that changes are planned or expected but it instead means that should a change occur, there is a plan ready to deal with such change. Dr. Miller commented that this is the right approach.

The approach to establishing specifications for each starting material was discussed. Pfizer's general approach for developing specifications for such relatively advanced starting materials is to use the knowledge of their synthesis, as well as their impurity profiles and associated fate-purge data, to develop specifications. For example, UK-453,464 is chiral and will therefore have a chiral test in its specification.

Dr. Miller said that from his perspective, knowledge of supplier processes is very positive. He noted that the Agency is in the process of implementing comments on the draft drug substance guidance and he sees many of these concepts in our approach. Dr. Ogilvie added that Pfizer has been very interested in the development of this guidance and Dr. Lin noted these approaches have been employed successfully with recent Pfizer candidates, citing darifenacin specifically.

Dr. Miller then said the Agency would consider the process upstream from the starting materials to be the responsibility of Pfizer and its vendors. Pfizer plans to identify the vendors in the submission but Dr. Miller stated this would not be required and that an update to the application will also not be required when vendor changes occur in the future. Dr. Miller also stated that referencing the information given on the _____ process in the IND and briefing document would be sufficient for the NDA. Dr. Ogilvie thanked Dr. Miller for this helpful information.

Dr. Ogilvie stated that with the control of unspecified impurities in _____ intermediates set at _____ we are proposing an acceptance criterion _____ maximum for unspecified impurities in the starting materials. He asked Dr. Miller if this is considered an acceptable position by the Division.

Dr. Miller said that, as seen from the questions sent to Pfizer, FDA had two main questions: 1) how well the process purges impurities from the two proposed starting materials and 2) why UK-408,026

was chosen as a starting material instead of UK-415,308 (the immediate precursor). He acknowledged, however, that Pfizer has presented a snapshot of what is current knowledge.

Dr. Miller noted that the endo-isomer is purged less efficiently and our response document gave levels of NMT [redacted]. He asked what levels have been seen recently. Dr. Robinson replied that while levels seen have correlated with the amount present in the starting material, which is not unexpected given its structural similarity to UK-427,857, none has been detected in the most recent batches of UK-408,026. Dr. Ogilvie added that purge is almost flat and we therefore expect this isomer to be a specified impurity in the starting material and drug substance. We plan to gather further fate-and-purge data for this and other impurities prior to finalizing suitable acceptance criteria.

Dr. Ogilvie summarized the general approach, that both quality and supply perspectives are considered. For previous candidates like voriconazole and darifenacin, impurities tended to purge. We try to understand which impurities are going to be important and the likelihood of structure and chemistry to enable purge from starting materials. In subsequent steps of the UK-427,857 synthesis, we are setting control at [redacted].

Dr. Miller replied that with a [redacted] limit for intermediates downstream, the Agency is comfortable with the proposed [redacted] limit for unspecified impurities in starting materials. He added this makes sense for compounds like this, when several steps yield [redacted] material. There followed a short discussion on general approaches, during which Dr. Lin noted the approach worked well for darifenacin, whose impurities were easy to purge. Dr. Miller noted that there is less concern about enantiomers because of the single chiral center.

Dr. Miller concluded that Pfizer's choice of two starting materials is justified. He asked if Pfizer might make the early precursors internally. Dr. Ogilvie replied that it was considered but it is currently expected that vendors will supply the starting materials.

Dr. Lin said more details are expected to be in the application in terms of process purge, [redacted] etc. Dr. Ogilvie said appropriate details will be provided in the NDA. Dr. Lin and Dr. Miller then noted that the CTD format does not lend itself easily to full inclusion of details. Dr. Ogilvie said Pfizer has used S.2.6 for development chemistry, with full details of impurity rationale (purge, etc.) in the specification rationale. Drs. Lin and Miller concurred with this approach.

Dr. Miller's questions on Appendix 1 (Process, supplier and change control for starting materials) of the premeeting package were then answered. In particular, Dr. Ogilvie confirmed that if new impurities are observed above the specification limit, Pfizer's initial approach would be to investigate their identity and fate-purge internally before discussions with the Agency, if necessary.

Drug Substance Specification

Dr. Ogilvie presented the drug substance specification strategy. Control of particle size distribution is not expected to be a critical quality attribute because the compound is highly soluble across the pH range and rapidly dissolves (within 15 minutes in 0.1N HCl). The manufacturing process and drug product performance will be assessed to determine whether particle size specification will be necessary. Dr. Miller replied that this is reasonable at this stage. The Agency will expect to review the data at pre-NDA stage. *CDER Comment:* Typically the pre-NDA discussions would focus on whether a test is appropriate, and evaluation of acceptance criteria would be part of the NDA review.

Dr. Ogilvie said only one polymorph is expected in manufactured material since the second polymorph found in screens is meta-stable and was only formed under conditions not found in the

synthesis. Further data will determine if the current proposal not to include a specification for a polymorph test can be supported. Dr. Miller said this is reasonable and if things change, perhaps the next step would be a suitable identity test, such as FT-IR.

Dr. Ogilvie said microbiological testing will be performed annually and if negative, this will not be included in the specifications. Dr. Miller stated that this is a standard approach and said the Division is comfortable with this proposal.

Drug Substance Stability

Dr. Ogilvie said a minimum of 12 months stability data on lots manufactured in Ringaskiddy will be available at time of filing.

He then reviewed a change made in the stability program since the premeeting package was submitted; this change was included with the recent responses to the FDA questions. Two registration stability lots underwent routine procedure and the third lot underwent a subsequent reprocessing step with [REDACTED]. This would give the option of using either isolation for the drug substance. Dr. Miller said this is a favorable approach, assuming the reprocessing does not affect product stability, i.e., data for the three lots do not diverge. Dr. Ogilvie emphasized that Pfizer had satisfactory development stability data on UK-427,857 isolated from [REDACTED] and said we may come back to the Division for further discussion should the data diverge.

Dr. Lin asked if we had USAN or INN names. Ms. Kapili said we have a proposed INN, maraviroc, which has been published but will not be final until December. We have therefore not used it in any of our documents to date.

Drug Product Formulation

Dr. Ogilvie described the differences between the clinical and commercial tablet formulations. The differences are minor changes: shape, color and debossing.

Based on previous experience, the team is also investigating the optimum level of magnesium stearate to facilitate commercial manufacture. Dr. Miller asked what properties are affected. Dr. Ogilvie replied that [REDACTED] properties might be optimized by adjusting magnesium stearate levels but these affect manufacturing efficiency and cosmetic appearance, not quality. Dr. Miller said they are aware of the need to optimize magnesium stearate but also know the level has affected product performance of some drugs.

Dr. Ogilvie said following SUPAC guidance, for a highly soluble, rapidly dissolving drug like UK-427,857, in vitro dissolution should be adequate to link the 75 and 150 mg commercial formulations to the clinical formulations. However, is it appropriate to use an in vitro approach to link the 300 mg commercial tablet to the 150 mg tablets used in clinical studies? Dr. Miller said the downside of a very rapidly dissolving tablet is the test may not be discriminatory and enquired about our strategy for developing a dissolution test. Dr. Ogilvie said that when dissolution profiles are first developed, one may want to end up with IV/IVC but we did not expect IV/IVC for UK-427,857. To get a suitable QC test, our approach is to explore a range of compendial media with conventional apparatus. Dr. Robinson added that the final test conditions will require careful selection, contrasting the very rapid dissolution observed in 0.1N HCl with incomplete dissolution observed at higher pH. We are doing more work to see if discriminatory conditions can be identified, however it is likely that the current release test (USP 1 baskets at 100 rpm with 0.01N HCl) will form the final test conditions.

Dr. Miller then asked for clarification on the specific point on which Pfizer was seeking advice. Dr. Ogilvie said that for 75 and 150 mg commercial tablets, there are direct links to clinical formulations with only minor changes in color, shape and debossing. For all three commercial strengths, the possible change in magnesium stearate levels could be managed by in vitro methods. However, we are considering what the best answer is for the correlation of the 150 mg clinical tablet to the 300 mg commercial tablet.

Dr. Arya asked if the increase in magnesium stearate was presented in the briefing document and Pfizer confirmed it was not. He said in vitro methodology should be acceptable provided the data show the same performance.

Dr. Lin said the formulations are linked by the common blend. The strength is dependent on the size of the tablet. The size depends on how hard the tablet is compressed. Dr. Lin stated that if a correlation could be established, for example, between hardness and dissolution, then it may be possible to make an in vitro extrapolation to the 300 mg tablet. Dr. Arya asked if there are any clinical data using the 300 mg tablet. Dr. Robinson said two 150 mg tablets are being used in the clinical studies to achieve the 300 mg dose. Dr. Lin asked if there are blood level data for the 300 mg tablet and Pfizer said no. The Pfizer Clinical and CMC teams are discussing whether a bioequivalence (BE) study will be necessary. Dr. Lin noted to Dr. Arya that there have been some instances when sponsors have been requested to perform a BE study. The Division agreed that an in vitro approach should first be tried and once data are obtained, there can be further discussion as to whether a BE study will be necessary.

Drug Product Process Development

Dr. Ogilvie presented the tablet composition, the three tablet strengths made from a common blend. The manufacturing process is standard and non-complex. Pfizer is working to identify the critical quality attributes and process parameters in collaboration with colleagues in commercial manufacturing. Appropriate details will be provided in the NDA. Dr. Lin advised a similar approach as that for the darifenacin CTD, whose P.2 section he considered well written.

Drug Product Specification

Dr. Ogilvie said the specifications are conventional for an immediate release tablet, in accordance with Q3B(R) and Q6A. We are continuing to gather data for attributes such as moisture, hardness, polymorphism, enantiomer content and microbiology to evaluate the need for specifications at time of NDA.

Dr. Miller said the Agency is considering whether there is a role for two types of dissolution criteria: a rapid QC test for routine drug product release and a discriminatory test to evaluate changes or for use as a periodic quality test. Dr. Miller stated that it would be advantageous to provide information on dissolution studies performed to date and Pfizer's approach to finalizing methodology during the IND phase, so that there was agreement on methodology used to collect drug product development data for the NDA. Dr. Robinson and Dr. Ogilvie agreed that an appropriate package would be submitted for review.

Dr. Arya asked if we had any permeability data. Dr. Robinson confirmed that UK-427,857 has low permeability, and is classified as a BCS class 3 compound.

Drug Product Stability

Dr. Ogilvie said drug product stability data is a key point for our discussion. In response to advice from the clinical reviewers, the program in treatment-experienced patients has been prioritized. According to current timelines, the clinical data may be ready to file when only 9-month drug product stability data are available, with 18-months' supporting data from closely related products. The 12-month data can be submitted during the review cycle.

Dr. Miller said it would be acceptable to file with 9-month stability data, with the understanding that the 12-month data would be submitted within 90 days of initial filing. Ms. Kapili asked for confirmation that this would not be considered a major amendment to the application that would trigger an adjustment to the review clock. Dr. Miller said as long as the 12-month data are submitted within 90 days, it would not affect the review clock, even for priority review. If the data are submitted closer to the action date, then it may lengthen the review cycle.

Dr. Ogilvie then asked if the clinical program goes very well and finishes ahead of current timelines, would filing with less than 9-month stability data be considered? Dr. Miller said that circumstance would need discussion between the Clinical and CMC reviewers before a decision can be made on the acceptability of less stability data.

Dr. Ogilvie then reviewed the registration stability program. Dr. Robinson confirmed that no detectable degradation has been seen. Dr. Ogilvie confirmed that the 9-month stability would include all stability attributes except microbiology and enantiomer assessments.

Bracketing Strategy

Clarification on the bracketing strategy was provided in the response to FDA comments. Dr. Ogilvie summarized the strategy: three lots of 300 mg and three lots of 75 mg will bracket one lot of 150 mg. We propose to evaluate only the bottle extremes [lowest and highest moisture vapor transmission rate (MVTR)] in the formal stability program.

Dr. Miller asked what correlates best with moisture uptake per tablet? Dr. Ogilvie said the detail of the approach can be provided to the Division. Dr. Miller said he would be very interested in getting such detail.

Dr. Robinson asked for comment as to whether it would be acceptable to put up only the "worst-case" transmission case instead of bracketing both extremes, given the good stability of the product observed to date. Dr. Miller said moisture uptake can affect physical properties like hardness but since it is hard to predict these effects at this stage, there may be value in also studying the more protected case. Dr. Lin added that studying both sides may provide valuable supporting data if significant changes are observed in one package. He therefore recommended bracketing at both ends. In response to Dr. Miller's question, Dr. Ogilvie confirmed that bracketing by MVTR is proposed within strengths but not across strengths.

Ms. Kapili summarized the key agreements and actions for Pfizer (see points in Executive Summary above). Since Pfizer agreed to provide dissolution data, Ms. Taylor suggested that data on lots with magnesium stearate be included. Dr. Miller said that would be very useful information and Pfizer agreed to include these data.

The Pfizer attendees thanked the reviewers for the informative discussion. It was agreed that future meetings can be done by teleconference or videoconference.

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

/s/

Marsha Holloman
6/17/05 02:05:57 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,229

Leilani V. Kapali, MA
Associate Director, Worldwide Regulatory Affairs
50 Pequot Avenue
New London, CT 06320

Dear Ms. Kapali:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Maraviroc (UK-427,857) Oral Tablet.

We also refer to your April 22, 2005, request for fast track designation submitted under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating Maraviroc (UK-427,857) oral tablet for treatment of HIV-1 infection as a fast track product.

We are granting fast track designation for the following reasons:

1. Maraviroc is being developed for treatment of HIV-1 infection, a serious and life-threatening disease.
2. Maraviroc's mechanism of action has the potential to fulfill an unmet medical need for HIV patients who have exhausted currently available therapeutic options.

If you pursue a clinical development program that does not support use of Maraviroc (UK-427,857) oral tablet for treatment of HIV-1 infection, we will not review the application under the fast track development program.

If you have any questions, call Kenny Shade, Regulatory Project Manager, at 301-827-2361 or 301-827-2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director

Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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On Original

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

/s/

Jeffrey Murray
4/29/05 11:09:55 AM

(ACTION PACKAGE CHECKLIST

Application Information		
BLA # n/a NDA # 22-128	BLA STN# n/a NDA Supplement # n/a	If NDA, Efficacy Supplement Type n/a
Proprietary Name: Selzentry™ Established Name: maraviroc Dosage Form: 150 mg & 300 mg Tablet		Applicant: Pfizer Inc.
RPM: Kenny Shade		Division: Antiviral Products Phone # 301-796-0807
NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): n/a Provide a brief explanation of how this product is different from the listed drug. n/a <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date		June 20, 2007
❖ Action Goal Date (if different)		Resubmission Goal Date September 25, 2007
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input type="checkbox"/> None <input checked="" type="checkbox"/> AE (June 20, 2007)
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): Type 1	
NDAs, BLAs and Supplements: <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input checked="" type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Information Alert

❖ Exclusivity	
<ul style="list-style-type: none"> NDA: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> NDA/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> NDAS: 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>) NDA: 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>) NDA: 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>) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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. 	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"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews).</i>) 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified
<ul style="list-style-type: none"> [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. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No

notice of certification?

(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 to the next section below (Summary Reviews).

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).

- (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?

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 written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p>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).</p> <p>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	June 18, 2007
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	
Labeling	
❖ Package Insert	Included
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	n/a
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	Included August 3, 2007
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	n/a
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	n/a
❖ Patient Package Insert	n/a
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	n/a
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	n/a
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	n/a
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	n/a
❖ Medication Guide	Included
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	n/a
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	n/a
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	n/a
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	n/a
❖ Labels (full color carton and immediate-container labels)	Included
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	n/a
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	Requested in action letter
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> DMETS 1/18/2007 & 5/9/2007 <input checked="" type="checkbox"/> DSRCS July 31, 2007 <input checked="" type="checkbox"/> DDMAC 1/18/2007 <input checked="" type="checkbox"/> SEALD June 7, 2007 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	Included
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If AP: OC clearance for approval 	n/a n/a
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
• Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)	Included in approval letter
• Incoming submission documenting commitment	June 5, 2007 submission and teleconferences held June 12 and August 3, 2007
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	Included
❖ Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	June 4, 2007
• Pre-NDA/BLA meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg November 28, 2006
• EOP2 meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg October 7, 2004
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	<input type="checkbox"/> No AC meeting
• Date of Meeting	April 24, 2007
• 48-hour alert or minutes, if available	Included
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	Included
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	Included
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
• <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
• <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout)	Date completed: June 11, 2007 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	Included
❖ 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 February 5, 2007
❖ ECAC/CAC report/memo of meeting	February 20, 2007
❖ Nonclinical inspection review Summary (DSI)	<input type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	Included
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	Included
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical 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

Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

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

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

/s/

Kenny Shade
8/6/2007 01:59:09 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET
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A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS PFIZER INC Jennifer Johnson 235 East 42nd Street New York NY 10017 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22-128
2. TELEPHONE NUMBER 212-733-8101	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME Celsentri (Maraviroc)	6. USER FEE I.D. NUMBER PD3006850
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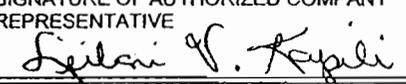
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

Public reporting burden for this collection of information is estimated to average 30 minutes 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 CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	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.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Director, WPAQA	DATE 17 NOV 2006
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
 \$896,200.00