

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-928

Administrative/Correspondence

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

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

NDA NUMBER

21-928

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)

CHAMPIX

ACTIVE INGREDIENT(S)

varenicline tartrate

STRENGTH(S)

0.5mg, 1.0mg

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

6890927

b. Issue Date of Patent

5/10/2005

c. Expiration Date of Patent

5/6/2022

d. Name of Patent Owner

Pfizer Inc.

Address (of Patent Owner)

235 East 42nd Street

City/State

New York, NY

ZIP Code

10017

FAX Number (if available)

Telephone Number

(212) 733-2323

E-Mail Address (if available)

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

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

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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

☐ Yes

☒ No

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
Comment: the patent claims the polymorph for which approval is sought as well as additional polymorphs.

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
Comment: this question is answered with respect to the polymorphs for which approval is not being sought (see 2.2).

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) 14 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 14 encompasses treating nicotine dependency, addiction and withdrawal by the administration of varenicline tartrate. The Indications and Usage section of the proposed labeling describes smoking cessation and so is covered by the claim.

5. No Relevant Patents

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

6. Declaration Certification

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

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

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

Date Signed

Bruce A. Pokras

June 14, 2005

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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a. United States Patent Number

6410550

b. Issue Date of Patent

6/25/2002

c. Expiration Date of Patent

11/13/2018

d. Name of Patent Owner

Pfizer Inc.

Address (of Patent Owner)

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10017

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

☐ Yes

☒ No

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

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

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

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

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

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) 13-14 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 13 encompasses reducing nicotine addiction or aiding in the cessation or lessening of tobacco use by the administration of varenicline. Claim 14 encompasses treating dependencies on, or addiction to, nicotine and tobacco products by the administration of varenicline. The Indications and Usage section of the proposed labeling describes smoking cessation and so is covered by those claims.

5. No Relevant Patents

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

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Date Signed

Bruce A. Pokras

June 14, 2005

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Check applicable box and provide information below.

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☒ 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

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

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88 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

EXCLUSIVITY SUMMARY

NDA # 21-928

SUPPL #

HFD # 170

Trade Name Chantix

Generic Name varenicline

Applicant Name Pfizer Inc.

Approval Date, If Known May 10, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒

NO ☐

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

505(b)(1)

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

YES ☒

NO ☐

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

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

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 ☐

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

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

Investigation #2

IND # YES ☐ NO ☐

Explain:

Page 6

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! 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: Dominic Chiapperino and Sara Stradley
Title: Regulatory Project Manager and CPMS
Date: May 10, 2006

Name of Office/Division Director signing form: Curtis Rosebraugh, MD, MPH
Title: Deputy Director, ODEII

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

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

/s/

Curtis Rosebraugh
5/10/2006 06:48:33 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-928 Supplement Type (e.g. SE5): _____ Supplement Number: (original submission)

Stamp Date: November 10, 2005 Action Date: May 10, 2006

HFD 170 Trade and generic names/dosage form: CHANTIX® (varenicline tartrate) 0.5 mg and 1 mg Tablets

Applicant: Pfizer Inc Therapeutic Class: 2030700

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: aid to smoking cessation treatment

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:

Min _____ kg _____ mo. _____ yr. 1 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 11 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:

Min _____ kg _____ mo. _____ yr. 12 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): 05/10/11

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:

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.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-928
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

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

Indication #2: Not Applicable

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:

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:

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:

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 Managercc: NDA ##-###
HFD-960/ Grace Carmouze**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 10-14-03)

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/s/

Dominic Chiapperino
5/10/2006 04:03:37 PM

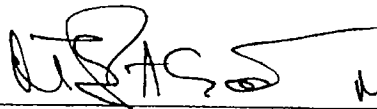
NDA 21928

CHAMPIX[®] (Varenicline Tartrate for Smoking Cessation)

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.

 M.-J. PAGE

Signature of Company Representative

20th September 2005

Date

PFIZER CONFIDENTIAL

MEMORANDUM

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

DATE: May 22, 2006

TO: File

FROM: Dominic Chiapperino

SUBJECT: **Record of correspondence to Sponsor regarding Phase IV
Commitments**

NDA 21-928, Chantix (varenicline)

Below are letters to and from Sponsor regarding requested Phase IV commitments:

**Appears This Way
On Original**

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Wednesday, May 10, 2006 3:05 PM
To: 'Page, Mike'
Subject: Phase IV commitments

Dear Mike:

These are the Phase IV commitments we believe are necessary to obtain from you.

1. To conduct a study to determine the multiple-dose pharmacokinetics of varenicline in pediatric patients in order to determine the appropriate doses for efficacy and safety evaluations in adolescent smokers, ages 12 through 16, inclusive, to determine the adverse event profile in adolescent patients and to establish whether there is any age group (or weight group) for whom varenicline is so poorly tolerated that its utility as an aid to smoking cessation treatment should not be evaluated in that group.

Final Report Submission: by November 10, 2007

2. To conduct a study to determine whether varenicline, as part of an overall smoking cessation program, is effective in achieving and maintaining smoking cessation in tobacco-addicted adolescents, ages 12 through 16, inclusive; to determine a safe and effective dose; and to document the ability of treating physicians to select appropriate patients. You will need to develop a means for determining reliable criteria for appropriate patient selection of tobacco-addicted teens so that teenage smokers who are not addicted will not be recruited, and so that labeling can convey these criteria to physicians who may wish to use the drug in adolescents.

Final Report Submission: by May 10, 2011

3. To conduct a study in pregnant women who are smokers and who are exposed to varenicline at the time of conception or any time during pregnancy. This information will be used to assess the potential risk to the mother, fetus and/or live born infant. Please refer to the Guidance for Industry: Establishing Pregnancy Exposure Registries in developing your protocol.

Protocol Submission: by November, 2006

Study Start: by May, 2007

Final Report Submission: by May, 2011

Please comment at your earliest convenience on these proposed studies.

Thanks,
Dominic

Dominic Chiapperino, Ph.D.
Regulatory Project Manager
FDA, Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology
Products
10903 New Hampshire Avenue
Building 22
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research



OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

Date: Wednesday, May 10, 2006
NDA: 21-928
Sponsor: Pfizer Inc.,
Proprietary Name: Chantix® (varenicline tartarate)
Author: Curtis J. Rosebraugh, MD, MPH, Deputy Director, ODE II

Planned Action: Approval (AP) pending resolution of any labeling issues.

Summary: This is a first cycle review for this new chemical entity, Varenicline, which is a non-nicotine, nicotine-receptor partial agonist. The signatory authority has been delegated to me by Dr. Robert J. Meyer, Director of ODE II.

This application is for approval of varenicline as a smoking cessation agent at a dose of 1 mg twice daily following a 1-week upward titration. The sponsor is advocating that the duration of therapy should be for 12-weeks, and for those patients that have successfully stopped smoking, an additional course of 12-weeks treatment increases the likelihood of long-term abstinence. It is believed that varenicline has its clinical effect by acting as a partial agonist at the $\alpha 4\beta 2$ nicotinic receptor subtype. In animal models, this receptor subtype has been demonstrated to be responsible for the reinforcing properties of nicotine.

The sponsor, as part of their develop plan, incorporated an active comparator, Zyban (bupropion hydrochloride, marketed by GlaxoSmithKline), which is the only other currently FDA approved non-nicotine smoking cessation product. At the time of filing, the Division's preliminary review of the efficacy studies indicated that varenicline may have substantial evidence to support a superiority claim compared to bupropion. Since this was deemed to represent a potential for a significant improvement of varenicline over existing therapies, the application received a Priority Review.

For detailed summaries of different disciplines, the reader is referred to reviews by Drs. Josefberg, Buenconsejo, Nallani, Zheng, De, Miller, Harapanhalli, Wang and Winchell. Dr. Winchell in particular has written an excellent team leader memorandum that goes into detail on all issues and therefore my memorandum will only briefly summarize the Agency's findings and my conclusions. The reader is also referred to the Division Director Memorandum written by Dr. Bob Rappaport, with which I'm in agreement.

Pfizer has provided data that clearly demonstrate efficacy for varenicline compared to placebo. During the review of clinical data, four issues have arisen which I will summarize here and discuss in more detail under the clinical section.

The first issue is whether varenicline should receive a superiority claim over bupropion. From my review of the data presented in the reviews, it appears that varenicline was tested against bupropion on a 'level playing field' and has clearly demonstrated greater statistical and clinically important efficacy. The design of the studies was consistent with those that allowed bupropion approval and should not have biased one drug over another. On that basis, I feel that the sponsors should be allowed to put the data from these studies in the label and claim superiority over bupropion.


The second issue is the dosing of varenicline. The sponsor has explored a variety of dosing regimens. It appears that the efficacy of the drug, as well as the most common adverse event (nausea), increases as the dose increases. This adverse event is not serious and, for the most part, did not limit subjects from completing a full course of therapy. The Division has had conversations with the sponsor regarding whether some type of patient-determined adjustable dosing schedule might be utilized to optimize the balance of efficacy with limiting adverse events. The sponsor has made a compelling argument based on the effect size for not lowering the usually recommended dose. The division now feels that the sponsor's position with its proposed dosing titration up to a regular dose of 1mg twice a day is sound. I agree with this conclusion.


The third issue is that, during the initial primary safety review, there was a question regarding whether there may have been a 'cardiac' signal based on ischemic and arrhythmic events. However, upon review of the cases and allowing for duration of exposure (in patient-years) instead of just counting raw events, the rates for varenicline and placebo are similar and the Division's review staff now feel the original concern for a cardiac 'signal' is not warranted.

The final issue is that the two major studies had very similar (almost identical) results for efficacy of varenicline, bupropion and placebo. Due to the remarkably similar results, these results were thoroughly investigated by the Division of Scientific Inspection (DSI), which included calling individual subjects for verification. DSI has concluded that the clinical data are accurate.

There seem to be no serious safety or potential clinical pharmacology drug-drug interaction safety issues identified with varenicline.

Based on the unanimous recommendation of the various review disciplines and my own review of the data, I recommend approval of varenicline pending negotiation of adequate labeling.

CMC: This application was reviewed 

 The Chemistry review team has determined that the CMC portion of the application is acceptable. The team has not identified any approvability issues regarding manufacture, process or sites with this product.

Pharm-Tox: No approvability issues were identified. However, the 2-year carcinogenicity studies revealed hibernoma (tumors of brown fat) in male rats at a mid range dose that is 31

times the human AUC at 1-mg twice a day. It is worth noting that varenicline did not have any mutagenic or clastogenic activity in several tests including the Ames test, chromosomal aberrations in cultured human lymphocytes, mammalian cell (CHO/HGPRT) gene mutation assay or in vivo rat micronucleus test. While this finding was not statistically significant, because of the rarity of this tumor in rats, Dr. De considered this finding treatment related, such that it should be included in labeling. The clinical significance of this is unknown, but considering that varenicline is not mutagenic and the exposure where this effect was first noticed in rats is 31 times that anticipated in human use, it is probably not relevant.

Clinical Pharmacology: Varenicline demonstrated linear pharmacokinetics with single or repeated doses of 1-3 mg/day. Radiolabel studies indicate that following oral administration the drug is almost entirely excreted in the urine. Permeability across the human gastrointestinal epithelium is high, not concentration-dependent and not mediated by known transport systems. Varenicline is not metabolized and does not inhibit or induce any major CYP-P450 isoenzymes. Varenicline has an average half-life of 20 hours, is renally excreted (unchanged), mainly through glomerular filtration with some active tubular secretion via the organic cationic transporter - OCT2. Varenicline has low affinity for this enzyme and clinically important drug-drug interactions through the OCT2 system are not anticipated. Varenicline exposure increases 1.5 fold in patients with moderate renal impairment and estimated creatinine clearances of ≥ 30 mL/min and ≤ 50 mL/min. In severe renal impairment (creatinine clearances < 30 mL/min), exposure was increased 2.1-fold and dosage adjustments should be made for patients with this degree (or worse) of renal impairment. Varenicline is efficiently removed by hemodialysis.

Since the timing of this application occurred during a transition period of Agency thinking on QT assessment, a formal QT study was not performed for this application (as would now be expected for almost all new molecular entities). Despite this, the sponsor has conducted a reasonably extensive pre-clinical (HERG channel and simian studies) and clinical evaluations that did not reveal any potential for QT prolongation. As such, the Clinical Pharmacology and Biopharmaceutics Review team is comfortable that this drug does not have QT prolongation potential. Further, since no drug-drug interactions have been demonstrated, even if a minor QT effect has not been detected, there appears to be little potential for significant accumulations of the drug that might worsen any minor effect.

Clinical/Statistical: The sponsor has provided six controlled clinical trials in the application in support of efficacy. The table below lists these studies (abbreviated from Dr. Winchell's review Pg. 9). Each of these six studies was of a randomized, parallel-group, double-blind, placebo-control design, with the exception of the maintenance study (A3051035). This maintenance study began as open-label treatment with varenicline, followed by randomization to double-blind varenicline or placebo (randomized withdrawal design).

Varenicline phase 2/3 efficacy studies			
Protocol type and #	Treatment Group, Regimen # of subjects		Duration of Treatment/Study
Phase 2 studies			
Dose-Ranging A3051002	Varenicline 0.3 mg QD 1 mg QD 1 mg BID Bupropion Placebo	N=126 N=126 N=125 N=126 N=123	6 weeks + 1 week placebo 7 weeks 7 weeks Optional follow-up 1 yr
Titration A3051007/1018	Varenicline 1 mg BID NT 1 mg BID T 0.5 mg BID NT 0.5 mg BID T Placebo	N=124 N=129 N=124 N=129 N=121	12 week Follow-up 1 yr from start of treatment
Flexible-dose A3051016/1019	Varenicline Flexible dosing 0.5 mg QD to 1 mg BID Placebo	N=157 N=155	12 week Follow-up 1 yr from start of treatment
Phase 3 studies			
Bupropion Comparator A3051028	Varenicline 1 mg bid Bupropion 150 mg bid Placebo	N=349 N=329 N=344	12 week Follow-up 1 yr from start of treatment
Bupropion Comparator A3051036	Varenicline 1 mg bid Bupropion 150 mg bid Placebo	N=343 N=340 N=340	12 week Follow-up 1 yr from start of treatment
Maintenance A3051035	OL Varenicline 1 mg bid DB Varenicline 1 mg bid Placebo	 N=602 N=604	OL: 12 week treatment with Varenicline DB: varenicline 1 mg BID or Placebo for 12 additional weeks. Nontreatment follow-up to 1 yr

Dr. Winchell has a very nice discussion of endpoints in her review and this topic will not be repeated here. The following table summarizes the primary efficacy criterion which is four-week continuous quit rate during the final four weeks of drug therapy and a secondary criterion of 52-week abstinence rate (adapted from Dr. Winchell's review Pgs 10,17).

Primary efficacy results and 52-week smoking abstinence rates							
Primary efficacy results	Varenicline 0.5 mg BID	Varenicline 1.0 mg BID	Varenicline Flexible	Bupropion	Placebo	Bupropion-Placebo	Varenicline 1 mg Bid-placebo
Study A3051028 (%)		44%		30%	17%	13%	27%
Odds Ratio				1.9	3.9		
Varenicline vs. Study A3051036 (%)		44%		30%	18%	12%	26%
Odds Ratio				1.9	3.8		
Varenicline vs. Study A3051035 (%)		51%*					
Study A3051007 (%)	45%	51%			12%		39%
Odds Ratio vs. placebo	6.1	7.8					
Study A3051016 (%)			40%		15%		35%
Odds Ratio vs. Placebo			5.7				
52-week smoking abstinence rate							
Study A3051028							
N(%)		74 (26%)		52 (17%)	27 (9%)	8%	17%
Study A3051036							
N(%)		74 (25%)		49 (19%)	34 (13%)	6%	12%
Study A3051035							
N(%)		247 (41%)			214 (35%)		6%
*Post-hoc calculation based on Weeks 8-12 during the open-label portion of study							

It is clear from these data that efficacy has been established for varenicline compared to placebo and that will not be discussed further. Study A3051035 allowed for an additional 12-weeks of dosing (in all successful quitters after an initial 12-weeks of therapy) in a blinded, randomized withdrawal design. This study demonstrated a greater success rate for smoking abstinence at 24-weeks (varenicline 70% vs. Placebo 50%, $p < 0.0001$, odds ratio 2.4) which would support the proposed labeling in the Dosage and Administration section of the label related to use for an additional 12 weeks beyond the initial 12 weeks in successful quitters. I have also included the 52-week quit rates, a secondary endpoint, in the table above to demonstrate the impressive fashion to which the efficacy advantage over placebo is sustained after drug therapy is stopped. It is also clear that bupropion demonstrated superiority to placebo and by about the same margin (with some caveats) as noted in others studies (referenced in Zyban's prescription label) that were used for its approval.

The table above highlights two issues identified by the division that deserve further discussion. Those issues are: 1) Should varenicline get a superiority claim to bupropion, and 2) should the recommended dosing for varenicline be 1mg BID or should it be a flexible dosing regimen (see study A3051016)?

Regarding the first issue, as discussed by Dr. Winchell, in order to get a superiority claim, it is important that bupropion be included in the studies in such a way that it is not disadvantage, but instead is used such that it has an unbiased potential to work (a level playing field). Dr. Winchell's review indicates that she is confident that bupropion was tested in a fair fashion. I think that this assessment is strengthened by the protocol designs that exclude previous users of bupropion, so as not to bias a study with known bupropion -unresponsive subjects. There is one protocol design that is not totally congruent with Zyban's 'Dosing and Administration' (D&A)

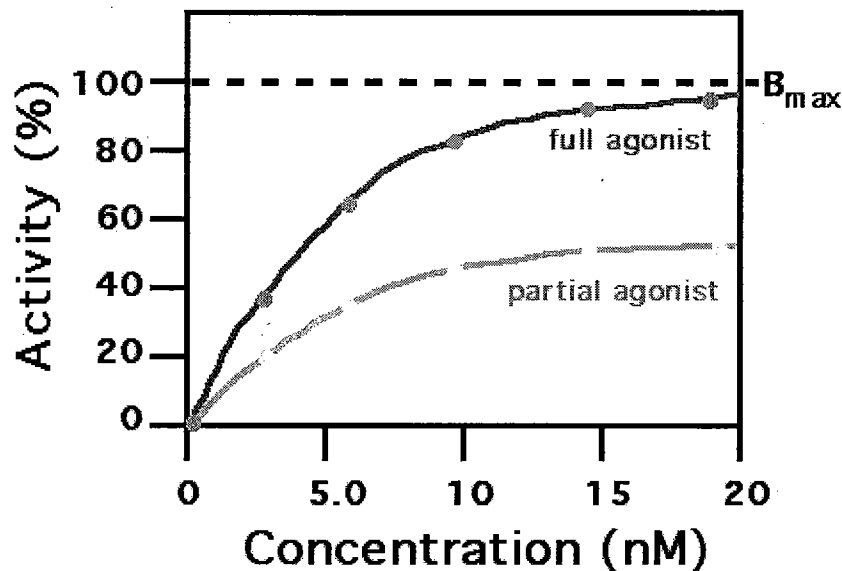
that I will comment on. The D&A section states that; “Patients should set a “target quit date” within the first 2 weeks of treatment with bupropion, generally in the second week”. In the two clinical trials listed above, a target quit date was set at 7 days instead of in the second week as is described in the Zyban label. The target quit date of 7 days is, however, still consistent with how the actual clinical study protocols were performed for the studies that are in Zyban’s label and lead to approval. Corporate memory does not exist for why the bupropion studies lead to labeling of a target quit date in the second week, as that is not how the bupropion studies were conducted. However, it is important to note that the studies above for varenicline that contained a bupropion arm were conducted in a fashion that would be suitable to demonstrate bupropion’s efficacy compared to placebo and would not, a priori, seem to favor one drug over another. I would also like to note that subjects were allowed a two week “grace” period on top of the one week target quit date, whereby smoking would not have counted as a failure thus allowing flexibility around the target quit date of 7 days. It is worth noting that the results with bupropion in these studies relative to placebo was similar to that seen in the original NDA for Zyban (11% relative quit advantage over placebo at 12 weeks for the 300 mg dose).

Regarding the second issue, the most common associated adverse event reported was nausea, which appeared to be dose related (as is the drug’s efficacy). Therefore, the issue is whether patients can self-titrate to find an effective dose that also minimizes nausea. The sponsor contends that the 1-mg bid dose offers the greatest chance of success in smoking cessation. Based on the data I have reviewed, I would agree with this statement. I also agree that even a small gain in effect size, when viewed in the context of the number of smokers in the United States and the significant health burden smoking causes upon the health care system, may have a significant health impact. It is also clear that a true self-titration schedule has not been adequately studied to the extent that one could determine this method of use to represent the optimal dosing scheme. Therefore, I agree with the sponsor’s proposed dosing recommendations. I would also encourage the sponsor to add clinical efficacy data from studies 02 and 07 in the Clinical Studies section and to allow for down-titration data in the Dosage and Administration section to allow for continued dosing in patients that cannot tolerate 1-mg BID due to adverse effects.

Because the efficacy results of the two major trials were so similar, the review team had DSI investigate whether the data submitted for the two studies were valid. Based on DSI’s investigation, it appears that the data from the two studies was accurately reported. The investigation included randomly contacting subjects to confirm their existence and that the data reported on their study records was correct.

The data available do not lead to a finding of any serious adverse events that are associated with varenicline. Initially, there was some debate by the review team regarding a possible numeric increase in cardiac events for drug vs. placebo. Upon reanalysis using person-years of exposure, there does not appear to any increase in ischemic and arrhythmic adverse events compared to placebo. The most common adverse events leading to discontinuation of therapy were nausea which occurred in approximately 3% of subjects, followed to lesser extents by headache and insomnia.

The Controlled Substances Staff (CSS) has determined that varenicline will not be scheduled. CSS did raise concerns about how the drug is being designated (i.e., a partial agonist at the $\alpha 4\beta 2$ nicotinic receptor subtype) in the labeling based on an animal self-administration (abuse) study that they felt demonstrated that this drug may have similar dependence findings to nicotine itself. However, these same studies demonstrate bupropion to have similar findings and bupropion has not been demonstrated to have any pharmacologic action at the nicotinic receptor. Therefore, it does not appear to me that a study designed to demonstrate that animals that self-administer varenicline to the same extent as they self-administer nicotine allows for drawing any conclusions about varenicline's pharmacologic role at a specific receptor. It should be noted in a Progressive Ratio schedule behavioral study, rats work much harder to get nicotine than varenicline suggesting that varenicline is less reinforcing than nicotine. Additionally, in a true pharmacologic sense, it would appear that animal self-administration studies do not allow for definition of a range of effects on the 'system' as one would expect to be able to demonstrate in a receptor study (see graph below that generically demonstrates a receptor study). As such, it does not seem that it would be possible to define a maximum effect for nicotine upon which to compare varenicline with any precision. I also note that 21CFR 201.57 specifies that the description section will have "the pharmacological or therapeutic class of the drug". This is defined by receptor studies and not animal behavior. Therefore, it does not appear to me that the animal studies override the in vitro receptor binding data and I believe the description of this product as a partial agonist is still warranted.



Review of patient reported outcomes by the Study Endpoints and Labeling Development Team (SEALD) has determined that of the additional patient reported claims sought by the sponsor, it would be appropriate to include "reduces urge to smoke" in the product label.

Data Integrity/Financial Disclosure: Data integrity was appropriate. There were a total of 805 investigators. Of these, 792 were certified as having no financial arrangements as defined in 21 CFR 54.2. Eleven investigators had financial information to disclose, representing the remaining

13 listed investigators (two had enrolled to multiple protocols, thus filing multiple FDA Form 3455). Two investigators held equity >\$50,000 and eleven received payments of other sorts. Re-analysis of efficacy data excluding data from these investigator sites did not change any efficacy findings.

Labeling/Nomenclature: DDMAC rejected the sponsors original name proposal (Champix) because they felt it would be promotional. DDMAC agrees with the present name proposed by the sponsor (Chantix).

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/s/

Curtis Rosebraugh
5/10/2006 12:53:33 PM
MEDICAL OFFICER



Global Research & Development

10 May 2006

Robert Rappaport, M.D., Director
Food and Drug Administration
Office of Drug Evaluation and II (ODEII)
Division of Analgesia, Anesthesia, and
Rheumatology Products
c/o Central Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

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PRIOR WRITTEN CONSENT OF PFIZER INC.

Dear Doctor Rappaport:

RE: NDA 21-928 (varenicline tartrate) tablets

General Correspondence: Post-Marketing Agreements (Clinical)

Reference is made to our above referenced pending New Drug Application for varenicline tartrate, submitted on November 10, 2005.

Pfizer hereby commits to the following Post-Marketing Agreements, as discussed in our teleconference today:

- 1) To conduct a study to determine the multiple-dose pharmacokinetics of varenicline in pediatric patients in order to determine the appropriate doses for efficacy and safety evaluations in adolescent smokers, ages 12 through 16, inclusive, to determine the adverse event profile in adolescent patients and to establish whether there is any age group (or weight group) for whom varenicline is so poorly tolerated that its utility as an aid to smoking cessation treatment should not be evaluated in that group.

Final Report Submission: by May 10, 2008

- 2) To conduct a study to determine whether varenicline, as part of an overall smoking cessation program, is effective in achieving and maintaining smoking cessation in tobacco-addicted adolescents, ages 12 through 16, inclusive; to determine a safe and effective dose; and to document the ability of treating physicians to select appropriate patients. Pfizer will develop a means for determining reliable criteria for appropriate patient selection of tobacco-addicted teens so that teenage smokers who are not

addicted will not be recruited, and so that labeling can convey these criteria to physicians who may wish to use the drug in adolescents.

Final Report Submission: by May 10, 2011

- 3) To conduct a prospective epidemiologic cohort study in pregnant women who are smokers and who are exposed to varenicline at the time of conception or any time during pregnancy. This information will be used to assess the potential risk to the fetus and/or live born infant. The study design and endpoints will be mutually agreed to by the FDA and Pfizer.

Protocol Submission: by November, 2006

Study Start by May, 2007

Final Report Submission: by May, 2011

Please contact me by telephone on (860) 715 1110 if you have any questions or require more information.

Sincerely yours,



Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance

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

/s/

Dominic Chiapperino
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CSO

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✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: May 8, 2006

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology
Products (HFD-170)

Through: Deborah B. Leiderman, M.D., Director
Michael Klein, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff (HFD-009)

Subject: I. Abuse liability assessment
II. Label review of Chantix (varenicline tartrate)
NDA 21-928
Submitted November 9, 2005
Indication: Smoking cessation
Sponsor: Pfizer, Inc.

I. Background:

The Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170) consulted CSS regarding the abuse potential of Chantix (varenicline tartrate).

Varenicline is proposed for the indication of smoking cessation. Varenicline is not currently marketed in any country. The recommended therapeutic doses are 0.5 - 1.0 mg (BID), taken as an oral capsule. In the clinical efficacy trials, varenicline (0.5-1.0 mg, BID or QD) was compared to both placebo and to 150 mg bupropion (Zyban), a drug that is marketed for the indication of smoking cessation.

The Sponsor proposes that varenicline not be controlled under CSA. They cite the results from non-clinical studies, clinical trials and human abuse potential studies in support of the position that varenicline does not have abuse potential.

Conclusions:

Varenicline acts as an agonist at the nicotinic receptor in whole animal behavioral tests, but acts as a partial agonist at the nicotine receptor in some neurochemical and electrophysiological tests measuring dopamine functioning. In humans, varenicline has therapeutic efficacy in reducing tobacco smoking in clinical trials, which suggests it is acting as an agonist substitute for nicotine.

Euphoria was reported in only 3 of 3,940 patients (< 1 out of 1000 patients) who participated in clinical trials. Gastrointestinal adverse events included nausea and vomiting, especially at higher doses (greater than 2 mg). In a human laboratory abuse liability study, varenicline did not produce either positive or negative subjective effects in smokers at 1 and 3 mg. However, in non-smokers, 1 mg varenicline produced some limited positive subjective effects that were accompanied by negative subjective effects.

There is some evidence of tolerance to varenicline in animals, but no evidence in clinical trials that patients increased their dose of varenicline to maintain therapeutic effects. Although there was no evidence of physical dependence in animals, patients in clinical trials who were abruptly discontinued from varenicline showed irritability, nicotine dependence and sleep disturbances, suggesting the presence of a mild withdrawal syndrome.

Recommendation:

Varenicline has a pharmacological profile most similar to that of nicotine, a drug that is not scheduled under the CSA. Based on the data in the present NDA, varenicline produces positive subjective effects in humans that are similar to those produced by two other unscheduled drugs marketed for smoking cessation, nicotine and bupropion. Therefore, CSS is not recommending that varenicline be scheduled under the CSA.

II. Recommendations for Product Label

The following language is recommended by CSS for the Description, Clinical Pharmacology/ Mechanism of Action, and Drug Abuse and Dependence sections of the product label for varenicline:

DESCRIPTION:

[

]

Note: CSS removed the Sponsor's designation that varenicline acts as a partial agonist at this receptor. Although biochemical data show that it does have partial agonist activity at

the $\alpha_4\beta_2$ nicotinic acetylcholine receptor, there are no behavioral data in animals or humans to support this designation. Instead, behavioral data in animals suggest that varenicline may be acting as a full agonist.

CLINICAL PHARMACOLOGY

Mechanism of Action

"Varenicline binds with high affinity [] and selectivity to the $\alpha_4\beta_2$ nicotinic acetylcholine receptor []

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Varenicline is not a controlled substance. *[Note: should not give the trade name as was done in the Sponsor version because substances are scheduled but products are not.]*

Humans: Fewer than 1 out of 1000 patients reported euphoria in clinical trials with varenicline. At higher doses (greater than 2 mg), varenicline produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of varenicline was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence.

In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers.

Animals: Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. []

[Varenicline pretreatment also
reduced nicotine self-administration.]

III. Data Review Summary of Submitted Studies

Receptor binding

Varenicline binds with high affinity ($K_i = 0.15$ nM) to the α -4, β -2 nicotinic receptor subtype of the acetylcholine receptor. According to the National Institute on Drug Abuse <<http://www.nida.nih.gov/researchreports/nicotine/nicotine.html>>, this receptor is thought to be responsible for the positive subjective effects of nicotine (Picciotto et al., 1998; Li et al., 2005). Based on electrophysiological studies in rats in comparison to nicotine (see below), varenicline acts as a partial agonist at the α -4, β -2 nicotinic receptor. Thus, in the treatment of smoking cessation, varenicline is being utilized therapeutically as an agonist substitute for nicotine.

Additionally, varenicline binds with moderate affinity ($K_i = 350$ nM) to the 5-HT₃ receptor, as an agonist. Since this receptor is associated with nausea (Dieras et al., 1990), it is probable that the high degree of nausea seen in non-smokers following varenicline administration occurs because of an additive or synergistic effect of nicotinic agonism and 5-HT₃ agonism.

In vitro neurochemistry

In electrophysiology studies using oocytes expressing α -4, β -2 nicotinic receptors, varenicline produced maximal current amplitudes that were less than half of those produced by nicotine. Although this in vitro test shows that varenicline is acting as a partial agonist at the α -4, β -2 nicotine receptor subtype, this test does not evaluate threshold currents necessary to produce behavioral effects (ie: the intrinsic activity of varenicline).

In a test of dopamine release in rodent striatal slices, a dose-range of varenicline produced 51% maximal efficacy compared to a fixed dose of nicotine. This demonstrates that varenicline produces partial agonism in this test.

In vivo neurochemistry

When dopamine turnover was measured in nucleus accumbens tissue from rats that had received systemic administration of varenicline or dopamine, the maximal response following a dose-range of varenicline was one-third that of a dose-range of nicotine. Additionally, pretreatment with varenicline reduced dopamine turnover produced by nicotine. Similarly, the nicotine antagonist, mecamylamine, reduced dopamine turnover

produced by nicotine or by varenicline. These data demonstrate that varenicline acts as a partial agonist in this neurochemistry test.

Extracellular measurement of dopamine release in freely moving rats was also tested using microdialysis. Varenicline produced a maximal response that was 63% that produced by nicotine. However, these two drugs were administered via different routes of administration (p.o. for varenicline vs. s.c. for nicotine), so these data cannot be used to determine relative efficacy of dopamine release, or whether varenicline is acting as a full or partial agonist. When varenicline was administered prior to nicotine administration, it reduced the dopamine release produced by nicotine. Similarly, mecamylamine reduced dopamine release induced by nicotine and by varenicline.

Preclinical behavioral tests of abuse liability

In animal behavioral studies, varenicline has behavioral effects that mimic those of nicotine. In rats trained to self-administer nicotine, varenicline is self-administered to the same degree or less than that of nicotine, depending on the work demands of the test. In drug discrimination tests, varenicline produces full generalization to the nicotine cue in rats. These whole animal tests demonstrate that varenicline behaves as a full nicotine agonist. No drugs other than nicotine were used as comparators against varenicline in these two behavioral tests.

Adverse events related to abuse potential in clinical efficacy trials

Notably, varenicline produced euphoria in only 3 of 3,940 patients (<1 out of 1000 patients, for a rate of < 0.1%). The adverse event profile observed in patients administered varenicline largely resembles that seen following nicotine administration. Psychiatric symptoms related to abuse liability reported in clinical efficacy trials include abnormal dreams (15.2% vs. 8.1% from placebo) and insomnia (35.2% vs. 22.0% from placebo). The rate of these two symptoms following varenicline administration was less than that produced by bupropion (Zyban) (45.2% and 11.9%, respectively) in the same trials. Gastrointestinal adverse events included nausea and vomiting, especially at higher doses (greater than 2 mg).

Human laboratory abuse liability study

In a human laboratory abuse liability study conducted with individuals who smoked and used stimulants, a single oral dose of 1 mg varenicline did not produce statistically significant increases in the positive or negative subjective measures. However, a single oral dose of the Schedule II drug, amphetamine (15 and 30 mg), produced statistically significant increases in positive and negative subjective responses in this subject population.

In contrast, in non-smoking individuals experienced with stimulants, a single oral dose of 1 mg varenicline produced increases in subjective responses for "good drug effects" and

"high" that were statistically significantly greater than placebo but less than those responses produced on the same scales by a single oral dose of amphetamine at 15 and 30 mg. Both varenicline (1 mg) and amphetamine (15 and 30 mg) produced greater increases in "bad effects" in non-smokers compared to placebo. However, in this subject population, only varenicline (1 mg) produced statistically significantly greater increases in "nausea" compared to placebo.

A 3 mg dose of varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers with a history of stimulant abuse. There were no positive subjective responses in smokers and a *decrease* in positive subjective responses in non-smokers.

Tolerance and physical dependence

Tolerance was not evaluated directly in the Phase 2/3 clinical studies. However, there are no data from these trials to suggest that patients were increasing their drug doses to maintain therapeutic effects over the course of the study. In rats, tolerance develops to the behavioral disruption induced by varenicline in an operant food task over a 14 day administration period. This suggests that tolerance may develop in humans to the adverse events that occur during initiation of varenicline administration.

No studies were conducted in humans to prospectively evaluate physical dependence. However, following abrupt discontinuation of 1 mg varenicline in clinical studies, there was an increase in some adverse events compared to placebo: irritability (3.6% vs. 0.2%) and sleep disorders/disturbances (2.8% vs. 0.2%). Given that these AEs are similar to those experienced by individuals during nicotine withdrawal, these symptoms may represent a varenicline withdrawal syndrome.

In contrast, in rats there was no evidence of withdrawal in the 5 days following discontinuation of varenicline after 14 day administration. Similarly, there are no withdrawal signs in monkeys treated for nine months with varenicline following drug discontinuation.

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APPENDIX A

Summary of Data Submitted in the NDA Related to Abuse Potential

I. Summary of Data Related to Abuse Potential from Human Studies

A. Human Laboratory Abuse Potential Study

A human laboratory abuse potential study was conducted in subjects with histories of stimulant abuse.

General Design

The purpose of this Phase 1, randomized, double-blind, crossover study was to compare the subjective and physiological effects following oral administration of: varenicline (1 and 3 mg), the Schedule II drug d-amphetamine (15 and 30 mg) and placebo. Subjects were required to have a negative urine test prior to participation in each study session. Subjects were inpatients for 36 hrs during each study period.

Each study session was separated by 7 days. This is an appropriate spacing between sessions, given that the half-life of varenicline is 24 hr and the half-life of amphetamine is 10-15 hr.

Subject Selection

A total of 45 male and female adults (18-55 years old) who were polydrug stimulant users were recruited for this study. All individuals must have recreationally used "amphetamine (or a pharmacologically similar drug such as methamphetamine)", plus at least one other drug on a minimum of 5 occasions within the past year. The majority of subjects appeared to have qualified for stimulant use on the basis of using both MDMA and cocaine, rather than use of amphetamine or methamphetamine. Nearly all subjects had extensive current experience with marijuana. Subjects were divided into smokers (n = 20 completers) and non-smokers (n = 21 completers).

Each subject participated in a screening session, the Amphetamine Qualifying Procedure. During this six hour session, they received (at 90 min intervals) placebo, 15 mg amphetamine, placebo and placebo. Subjects were tested for subjective response using VAS-Drug Liking, VAS-High, ARCI-Abuse Liability and Multiple Choice Procedure. Criteria for participation in the full study was based on subjects having a correlation of 0.7 between the profile shape of the expected curve (0 for placebo and 1 for amphetamine) and the actual response curve on at least half of the 4 subjective measures. CSS has previously informed the Sponsor that we are aware that the MCP is not a validated scale.

The exclusion criteria were standard for psychoactive drug studies and included exclusion of subjects who had acute or chronic disease, exposure to investigational drugs, and

physical dependency on any drug or alcohol. Women who were pregnant or lactating were also excluded.

Drug Administration

Subjects were required to ingest a total of 10 capsules in each test condition, consisting of 0-6 active drug capsules and 4-10 placebo capsules. Varenicline capsules contain 0.5 mg of the drug, so subjects ingested 2-6 capsules (1-3 mg total). Amphetamine capsules contain 5-10 mg of the drug, so subjects ingested 2-3 capsules (15-30 mg total).

Data Collected During Study

Subjective responses were taken at baseline and at 1, 2, 3, 4, 6, 8 and 24 hr after drug administration. These subjective measures included Visual Analog Scales (Drug Liking, Good Effects, High, Pleasant Mental Feeling, Pleasant Physical Feeling, Bad Effects, Nausea), ARCI scales (Amphetamine, Benzedrine, Stimulant/Euphoria, Stimulant/Motor, LSD/Dysphoria, Unpleasant/Dysphoria, Unpleasant/Physical). The Multiple Choice Procedure, a measure known to CSS to not be validated, was also given at 8 hr post-dose.

Results

Amphetamine Qualifying Procedure

All subjects accepted to participate in the study had a statistically significant positive response to 15 mg amphetamine compared to placebo on the VAS-Drug Liking, VAS-High and ARCI-Abuse Potential subjective measures. This was true for both smokers and non-smokers, although smokers consistently had slightly lower positive responses to amphetamine. These data confirm that even though most potential subjects had experience with MDMA and cocaine (rather than amphetamine or methamphetamine), they did show a positive subjective response to 15 mg amphetamine.

Abuse Liability Study Comparing Varenicline to Amphetamine

Study Validation: Response to Amphetamine

Acute oral doses of the Schedule II drug, amphetamine (15 and 30 mg), produced statistically significant increases in response compared to placebo on the positive subjective scales of VAS-Drug Liking, VAS-Good Effects, VAS-High, VAS-Energized, VAS-Pleasant Mental and VAS-Physical Effects for both smokers and non-smokers. This differentiation from placebo with a known drug of abuse validates the use of the subjective measures for evaluating abuse liability.

Additionally, in smokers, there were statistically significant increases in response compared to placebo on the following negative subjective scales: VAS-Bad Effects,

VAS-Nausea, VAS-Fatigue, ARCI-LSD, ARCI-Unpleasant/Dysphoria, ARCI-Unpleasant-Physical. In contrast, in non-smokers, there were no statistically significant increases in any negative subjective VAS scale or in ARCI-Unpleasant/Dysphoria, although there was a statistically significant increase in ARCI-LSD and ARCI-Unpleasant/Physical.

Adverse events included euphoric mood, which was observed in 2 of 20 subjects (10%) following 15 mg amphetamine and in 6 of 20 subjects; 29%) following 30 mg amphetamine.

Response to Varenicline, Amphetamine and Placebo in Smokers and Non-Smokers

Summarized data from smokers and non-smokers are found in Appendix B.

** Smokers' Response to 1 mg Varenicline*

Smokers (n = 20 completers) did not show a statistically significant difference from placebo on any of the positive or negative VAS subjective scales or on any of the positive or negative ARCI subjective scales. (Thus, no individual data are provided for smokers).

Similarly, in smokers there were no reports of euphoria following varenicline, although adverse events did include nausea, vomiting and headache. These results are probably the result of smokers' tolerance to the effects of nicotinic drugs such as varenicline.

** Non-Smokers' Response to 1 mg Varenicline*

Varenicline produced both positive and negative subjective effects in non-smokers (see individual data charts in Appendix C). Non-smokers (n = 21 completers) had a statistically significant increase in response compared to placebo following acute administration of 1 mg varenicline on two positive subjective scales selected as primary measures: VAS-Good Effects and ARCI-Abuse Potential. There was also a statistically significant increase in response compared to placebo on four other positive subjective scales designated as secondary measures: VAS-High, ARCI-Amphetamine, ARCI-Stimulation/Euphoria, ARCI-Stimulation/Motor. The Sponsor states in the narrative that the VAS-High result should be interpreted as measuring "feel drug effect". However, the VAS-High scale has been validated as measuring pleasurable effects related to abuse liability in many other studies using a variety of known drugs of abuse.

In this population, there was no statistically significant differences from placebo on the following positive subjective measures, designated as secondary for statistical analysis: VAS-Drug Liking, VAS-Energized, VAS-Pleasant Mental Effects and VAS-Pleasant Physical Effects, and ARCI-Benzedrine

On negative scales, there was a statistically significant increase in response compared to placebo for VAS-Nausea, ARCI-LSD, ARCI-Unpleasant/Dysphoria, ARCI-Unpleasant-

Physical. However, there were no significant increases in VAS-Bad Effects or in VAS-Fatigue.

Additionally, in non-smoking subjects, one of the most frequently reported adverse events included euphoric mood from 1 mg (n = 2 of 21 subjects; 10%) and from 3 mg (n = 2 of 21 subjects; 10%). This rate was similar to that seen following 15 mg amphetamine (n = 2 of 20 subjects; 10%), although lower than that from 30 mg amphetamine (n = 6 of 20 subjects; 29%). Additional adverse events in non-smoking subjects included headache, nausea, vomiting and dizziness, which are known adverse events associated with stimulation of the nicotine receptor.

** Smokers and Non-Smokers Response to 3 mg Varenicline*

The most prominent response to 3 mg varenicline in both smokers and non-smokers was a statistically significant increase in negative effects, as measured by VAS-Bad Effects, VAS-Nausea, ARCI-LSD, ARCI-Unpleasant/Dysphoria, ARCI-Unpleasant-Physical. These results are consistent with the adverse event profile observed in clinical efficacy trials.

Additionally, in non-smokers, there were significant *decreases* compared to placebo on such positive subjective effects as VAS-Pleasant Mental Effects and VAS-Pleasant Physical Effects, ARCI-Abuse Potential and ARCI-Benzedrine. However, there was a significant increase in response compared to placebo on VAS-Energized in non-smokers.

In contrast to non-smokers, smokers showed no significant positive responses to the 3 mg dose of varenicline.

Conclusions

Consistent with the data from clinical trials in smokers, administration of 1 mg varenicline to smokers in this human laboratory abuse liability study did not produce any significant positive or negative responses. In contrast, at 3 mg, smokers show a preponderance of negative effects, including nausea. Since varenicline is a nicotine agonist, the lack of positive response in smokers is probably the result of regulation of the nicotinic receptor through chronic exposure to nicotine.

In contrast, in non-smokers, administration of 1 mg varenicline produced some positive effects as well as some negative effects. Although these positive responses were approximately twice that of placebo, they were less than those produced by the Schedule II drug, amphetamine, at 15 and 30 mg, where the response was three or more times greater than that from placebo. Additionally, the negative responses to 1 mg varenicline was 300% greater than placebo, while the negative responses to amphetamine were only 50% greater than placebo.

The data from this study do not suggest that varenicline has abuse liability.

B. Adverse Events in Clinical Efficacy and Safety Studies

When varenicline was tested in 3,940 patients in Phase 2/3 clinical studies in which the majority of subjects received doses from 0.5 - 1.0 mg BID, two adverse events emerged of interest to an abuse liability assessment: abnormal dreams (13.8% vs. 6.7% from 150 mg bupropion and 5.0% from placebo) and insomnia (19.1% vs. 22.6% from 150 mg bupropion and 12.7% from placebo). Neither of these AEs indicate abuse liability in the absence of evidence that varenicline produces rewarding responses, such as euphoria.

Euphoria was reported rarely in any clinical trial. In Phase 2/3 trials, varenicline produced three incidents of euphoria (1 mg QD in 2 patients, 1 mg BID in 1 patient), bupropion produced two incident of euphoria (150 mg), and there were no incidents of euphoria following placebo administration. Thus, the rate of euphoria resulting from varenicline administration was less than 1 in 1000 patients.

In Phase 1 trials, there were two incidents of euphoria, both involving bupropion, co-administered with either placebo or varenicline (0.5 mg).

C. Pharmacokinetics in Clinical Trials

The Tmax of the varenicline is 3-4 hr following oral administration. Varenicline is predominantly absorbed unchanged and 91% is excreted unchanged, primarily in the urine. The elimination half-life of varenicline is 24 hr.

D. Physical Dependence and Tolerance in Clinical Efficacy/Safety Trials

The Sponsor stated that no prospective tolerance or physical dependence studies were conducted in humans. However, abrupt discontinuation of 1 mg varenicline was evaluated for 7 days in patients in clinical trials, using the Minnesota Nicotine Withdrawal Scale (MNWS) and standard AE evaluations.

Data from the MNWS and AE data show that abrupt discontinuation of 1 mg varenicline produces an increase (compared to placebo) in the following AEs: irritability (3.6% vs. 0.2%) and sleep disorders/disturbances (2.8% vs. 0.2%). Given that these AEs are similar to those experienced by individuals during nicotine withdrawal, these symptoms may represent a varenicline withdrawal syndrome.

II. Summary of Data Related to Abuse Potential from Preclinical Studies

A. Chemistry and Receptor Binding

The chemical name for varenicline is 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate. Its molecular formula is C₁₃H₁₃N₃ and molecular weight is 361.35. It is highly soluble in water.

The receptor selectivity of varenicline was evaluated using a standard binding battery of CNS sites. These studies showed that varenicline binds with high affinity to the alpha-4, beta-2 subtype of the nicotine cholinergic receptor. Varenicline is a full agonist at this site, based on whole animal behavioral studies.

Additionally, varenicline binds with moderate affinity ($K_i = 350$ nM) to the 5-HT₃ receptor, as an agonist. Since this receptor is associated with nausea (Dieras et al., 1990), it is probable that the high degree of nausea seen in non-smokers following varenicline administration occurs because of an additive or synergistic effect of nicotinic agonism and 5-HT₃ agonism.

B. Metabolites

Following oral administration, varenicline produces only minor metabolites (less than 8%). These compounds were not characterized in binding studies or behaviorally.

C. Preclinical Neurochemistry

In vitro neurochemistry

In electrophysiology studies using oocytes expressing alpha-4,beta-2 nicotinic receptors, varenicline produced maximal current amplitudes that were less than half of those produced by nicotine. Although this in vitro test shows that varenicline is acting as a partial agonist at the alpha-4,beta-2 nicotine receptor subtype, this test does not evaluate threshold currents necessary to produce behavioral effects (ie: the intrinsic activity of varenicline).

In a test of dopamine release in rodent striatal slices, a dose-range of varenicline produced 51% maximal efficacy compared to a fixed dose of nicotine. This demonstrates that varenicline produces partial agonism in this test.

In vivo neurochemistry

When dopamine turnover was measured in nucleus accumbens tissue from rats that had received systemic administration of varenicline or dopamine, the maximal response following a dose-range of varenicline was one-third that of a dose-range of nicotine. Additionally, pretreatment with varenicline reduced dopamine turnover produced by nicotine. Similarly, the nicotine antagonist, mecamylamine, reduced dopamine turnover produced by nicotine or by varenicline. These data demonstrate that varenicline acts as a partial agonist in this neurochemistry test.

Extracellular measurement of dopamine release in freely moving rats was also tested using microdialysis. Varenicline produced a maximal response that was 63% that produced by

nicotine. However, these two drugs were administered via different routes of administration (p.o. for varenicline vs. s.c. for nicotine), so these data cannot be used to determine relative efficacy of dopamine release. When varenicline was administered prior to nicotine administration, it reduced the dopamine release produced by nicotine. Similarly, mecamylamine reduced dopamine release induced by nicotine and by varenicline.

D. Preclinical Behavioral Studies

Self-Administration

Self-administration assesses the rewarding properties of a drug. If animals actively work at a behavioral task in order to receive a dose of the drug, it is likely that the drug will be rewarding in humans. A good correlation typically exists between those drugs that are self-administered by laboratory animals and those that are abused by humans (Balster and Bigelow, 2003).

Varenicline (1, 10, 30, 56, 100, 320 mcg/kg/infusion) was self-administered by rats (n = 3) trained to self-administer nicotine (30 mcg/kg/infusion) using a fixed ratio (FR5) schedule of reinforcement. At 10 and 56 mcg/kg/infusion, varenicline was self-administered at a level that was approximately 95% of the responding for 30 mcg/kg/infusion of nicotine. Other doses produced non-linear degrees of responding ranging from 42-85% responding for 30 mcg/kg/infusion of nicotine. When the same doses of nicotine (1, 10, 30, 56, 100, 320 mcg/kg/infusion) were available to rats (n = 5), there was a similarly variable and non-dose dependent pattern of self-administration, with 10 and 30 mcg/kg/infusion being the only doses that produced responding equal to or greater than 95% responding to 30 mcg/kg/infusion of nicotine.

In contrast, when a progressive ratio schedule of reinforcement was used, varenicline (1, 10, 30, 56, 100, 320 mcg/kg/infusion) was self-administered by rats trained to self-administer nicotine (30 mcg/kg/infusion) to a lesser degree than nicotine itself. Responding to nicotine effectively plateaued at 30, 56 and 100 mcg/kg/infusion (with ~150 lever presses/session), with less than 63 bar presses/session at higher and lower doses. Varenicline produced a peak response rate of ~63 bar presses/session at 56 mcg/kg/infusion, with less than 40 bar presses/session at higher and lower doses. Thus, varenicline may have less rewarding effects than nicotine.

Additionally, in a separate study, pretreatment with varenicline (1, 1.78, 3 mg/kg, s.c.) significantly reduced nicotine self-administration (30 mcg/kg/infusion).

Drug Discrimination

Drug discrimination is a method in which animals indicate whether a test drug produces physical sensations similar to those produced by a known psychoactive drug (Balster and Bigelow, 2003).

In rats trained to discriminate 0.4 mg/kg nicotine, varenicline produced full generalization at 1.0 mg/kg (highest dose tested), with linear degrees of generalization at doses between 0.01 to 0.3 mg/kg.

E. Preclinical Physical Dependence and Tolerance

Varenicline reduced the response rate in an operant food task in rats on Day 1, with a reduction in the behavioral interference over the course of 14 day drug administration. Thus, varenicline produces tolerance to this effect.

Upon discontinuation of varenicline after 14 days, there was no change in the response rate in the same operant food task or in general behavior. This suggests no signs of withdrawal, and therefore no physical dependence.

There were no signs of withdrawal in the 5 weeks following discontinuation of 0.1, 0.2 or 0.6 mg/kg (BID) in 9 month monkey study.

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Appendix B
Summarized Data from Human Laboratory Abuse Liability Study

Variable Analog Scales (VAS) -- mean peak scores

*(P = placebo, A = amphetamine, V = varenicline, number = mg/dose, * = $p < 0.05$)*

Non-Smokers

	P	A15	A30	V1	V3
Good Effects	18	55*	69*	40*	16
High	21	55*	67*	41*	35
Energized	28	54*	68*	44	34*
Pleasant Mental	51	64*	73*	55	46*
Pleasant Physical	51	70*	63*	55	43*
Bad Effects	12	20	26	30	71*
Nausea	10	9	8	29*	74*
Fatigue	38	33	27	44	64*

Smokers

	P	A15	A30	V1	V3
Good Effects	15	58*	78*	23	20
High	15	54*	71*	22	19
Drug Liking	51	64*	77*	52	42
Energized	31	64*	75*	42	35
Pleasant Mental	53	60	70*	55	52
Pleasant Physical	53	64*	73*	54	53
Bad Effects	14	30*	34*	17	43*
Nausea	3	10	15*	8	44*
Fatigue	58	46	37*	44	67

Addiction Research Center Inventory (ARCI) scales -- peak scores*(P = placebo, A = amphetamine, V = varenicline, number = mg/dose, * = $p < 0.05$)***Non-Smokers**

	P	A15	A30	V1	V3
Abuse Potential	20	25*	27*	23*	18*
Amphetamine	7	14*	19*	11*	8
Benzedrine	16	21*	24*	18	14*
Stim/Euphoria	5	17*	24*	10*	4
Stim/Motor	3	5*	7*	5*	3
LSD	10	15*	19*	15*	18*
Unpleas/Dysphoria	3	4	5	5*	9*
Unpleas/Physical	3	4	6*	5*	11*

Smokers

	P	A15	A30	V1	V3
Abuse Potential	22	25*	26*	22	20
Amphetamine	9	16*	20*	10	9
Benzadrine	17	21*	23*	18	16
Stim/Euphoria	6	17*	23*	8	6
Stim/Motor	3	6*	7*	3	3
LSD	10	16*	20*	11	13*
Unpleas/Dysphoria	3	5*	6*	3	6*
Unpleas/Physical	3	5*	6*	3	7*

APPENDIX C**Individual Data from Non-Smokers in Human Laboratory Abuse Liability Study****Non-Smokers****VAS "Good Effects"**

<u>Subject</u>	<u>Varen 1 mg</u>	<u>Amph 15 mg</u>	<u>Amph 30 mg</u>	<u>Placebo</u>
014	9	67	81	13
022	0	2	41	2
023	2	73	0	58
024	92	95	68	2
025	31	11	52	19
026	0	13	23	2
029	52	62	67	65
048	44	50	54	0
049	0	75	100	0
071	51	64	62	15
079	50	62	60	30
082	55	84	90	52
092	54	0	96	0
098	50	56	58	50
120	51	64	93	4
121	37	86	82	0
123	45	55	76	51
124	23	1	79	0
129	56	79	92	0
130	87	70	99	10
mean	39.8	54.7	68.7	17.8
S.D.	26.3	30.4	26.2	23.0

greater than placebo (n = 20)

11	13	17
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Non-Smokers**VAS "High"**

<u>Subject</u>	<u>Varen 1 mg</u>	<u>Amph 15 mg</u>	<u>Amph 30 mg</u>	<u>Placebo</u>
014	10	62	85	50
022	1	1	28	1
023	0	80	0	0
024	80	80	67	2
025	20	50	52	50
026	0	12	26	2
029	52	67	70	63
048	56	51	54	1
049	0	60	94	0
071	51	55	60	49
079	51	61	61	9
082	60	80	79	50
092	55	51	81	50
098	50	25	79	61
120	60	62	82	3
121	22	80	89	0
123	64	54	70	51
124	44	5	78	0
129	56	82	92	0
130	77	69	92	1
mean	40.7	55.3	67.0	21.1
S.D.	26.0	24.8	24.9	25.9

greater than placebo (n = 20)

10

12

18

Non-Smokers**VAS "Drug Liking" (scale is neutral = 50)**

<u>Subject</u>	<u>Varen 1 mg</u>	<u>Amph 15 mg</u>	<u>Amph 30 mg</u>	<u>Placebo</u>
014	50	65	83	50
022	37	17	47	38
023	50	77	51	50
024	86	81	61	51
025	51	53	51	51
026	50	61	70	52
029	50	63	73	50
048	11	50	57	50
049	50	60	99	50
071	51	65	51	50
079	51	47	60	50
082	61	100	100	52
092	57	50	88	50
098	51	55	57	50
120	50	65	97	50
121	50	83	92	50
123	36	56	79	53
124	50	51	88	51
129	55	77	88	50
130	83	68	99	50
mean	51.4	63.2	74.5	47.5
S.D.	14.9	17.3	18.9	11.3

greater than placebo (n = 20)

2

10

12

Non-Smokers**ARCI "Abuse Potential"**

<u>Subject</u>	<u>Varen 1 mg</u>	<u>Amph 15 mg</u>	<u>Amph 30 mg</u>	<u>Placebo</u>
014	20	28	28	18
022	19	19	23	17
023	20	31	19	19
024	32	29	27	19
025	24	23	22	20
026	18	19	24	18
029	21	28	27	24
048	20	20	21	20
049	24	29	31	23
071	20	22	23	21
079	22	26	22	21
082	26	28	33	23
092	29	23	27	20
098	23	24	29	21
120	23	31	34	21
121	28	25	25	19
123	23	28	32	26
124	18	18	28	19
129	24	26	29	21
130	30	27	28	18
mean	23.1	25.3	26.6	20.4
S.D.	4.0	4.0	4.2	2.3

greater than placebo (n = 20)

4

8

12

Non-Smokers**VAS "Bad Effects"**

<u>Subject</u>	<u>Varen 1 mg</u>	<u>Amph 15 mg</u>	<u>Amph 30 mg</u>	<u>Placebo</u>
014	10	50	59	8
022	12	2	1	1
023	0	13	0	40
024	2	1	0	2
025	8	20	54	35
026	0	0	0	0
029	55	57	61	39
048	56	50	50	0
049	0	0	0	0
071	66	15	3	6
079	62	40	66	23
082	50	50	2	1
092	0	0	2	19
098	0	0	0	50
120	53	38	0	3
121	0	12	65	0
123	70	7	17	2
124	50	1	50	0
129	8	16	97	0
130	62	23	0	23
mean	29.7	19.9	26.4	12.0
S.D.	28.6	19.7	32.1	16.4

greater than placebo (n = 20)

11	10	9
----	----	---

References

Balster RL and Bigelow GE (2003). Guidelines and methodological reviews concerning drug abuse liability assessment. Drug and Alcohol Dependence 70: S13-S40.

Dieras V, Extra JM, Le Bonniec M, Madelaine I, Espie M, Marty M. 5HT3-antagonist receptors: their role in drug-induced emesis. Nouv Rev Fr Hematol. 1990;32(6):449-52.

Li MD, Beuten J, Ma JZ, Payne TJ, Lou XY, Garcia V, Duenes AS, Crews KM, Elston RC. Ethnic- and gender-specific association of the nicotinic acetylcholine receptor alpha4 subunit gene (CHRNA4) with nicotine dependence. Hum Mol Genet. 2005 May 1;14(9):1211-9.

Picciotto MR, Zoli M, Rimondini R, Lena C, Marubio LM, Pich EM, Fuxe K, Changeux JP. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. Nature. 1998 Jan 8;391(6663):173-7.

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/s/

Katherine Bonson
5/8/2006 05:46:48 PM
PHARMACOLOGIST

Deborah Leiderman
5/8/2006 06:10:18 PM
MEDICAL OFFICER

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

Date: May 8, 2006

To: Bob Rappaport, M.D., Director
Division of Analgesia, Anesthesia & Rheumatology Products
(HFD-170)


Through: Deborah B. Leiderman, M.D., Director
Controlled Substance Staff (HFD-009)

From: Michael Klein, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

Subject: Executive Summary
Abuse Liability Assessment of NDA 21-928
Varenicline 0.5 & 1 mg Tablets (called CP-526,555 under IND 58,994)
Submitted: November 9, 2005; Sponsor: Pfizer, Inc.

Background:

The Controlled Substance Staff (CSS) was asked to assess the abuse liability of varenicline (NDA #21-928) by the Division of Analgesia, Anesthesia, and Rheumatology Products (HFD-170).

Varenicline tartrate is a new chemical entity developed by Pfizer as an aid in smoking cessation. Varenicline is described as a full and partial nicotinic agonist, and selective for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtype. Varenicline is formulated as an immediate release (IR) film-coated tablet. 

¹ Varenicline has not been approved for marketing approval anywhere in the world.

The proposed rationale for the use of varenicline in smoking cessation is based on published literature indicating that the $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtype mediates nicotine's dependence producing effects and provides relief from craving and withdrawal symptoms. Additionally, a partial agonist would be expected to block the behaviorally reinforcing effects of exogenous nicotine.

Conclusion:

Varenicline does not exhibit the chemical structure, pharmacology, or profile of effects of a drug of abuse or one that is currently controlled under the Controlled Substances Act

(CSA). Varenicline exhibits a profile of neuropsychiatric adverse events similar to those of nonscheduled drugs, nicotine and bupropion. The review by Dr. Katherine Bonson, Pharmacologist (CSS), contains proposed language for the product label **Drug Abuse and Dependence** section.

Data Review and Discussion:

The abuse liability assessment of varenicline is described below. Issues that are related to the abuse liability of varenicline include the following:

1. Receptor binding and CNS pharmacology

Varenicline is highly selective and binds more potently to the $\alpha_4\beta_2$ receptor subtype than to other common nicotinic receptors (>500-fold $\alpha_3\beta_4$ > 3500- fold α_7 , >20,000-fold $\alpha_1\beta\gamma\delta$), or to non-nicotinic receptors and transporters (>2000-fold). Varenicline functions as a partial agonist in both *in vitro* and *in vivo* models of nicotinic receptor function. The $\alpha_4\beta_2$ subtype of the neuronal nicotinic receptor is believed to mediate the behaviorally reinforcing effects of nicotine. Varenicline activates the mesolimbic dopamine system to levels only about 50% of those induced by nicotine. Varenicline blocks nicotine's ability to activate the $\alpha_4\beta_2$ receptor and stimulate the central nervous mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking.

2. Preclinical /Animal Pharmacological Behavioral Studies

Varenicline generalized to a nicotine cue in drug discrimination studies, and reduced the amount of nicotine that rats self-administered. Pfizer contends that varenicline does not produce detectable withdrawal effects in animal models.

In animal pharmacology/toxicology studies, the major target organs were brain/central nervous system (CNS), gastrointestinal tract (GI), and lymphoid system. Effects were also observed in the cardiovascular and hepatic systems. CNS and gastrointestinal clinical signs were noted sporadically in all dose groups in all species studied. Similar clinical signs were predicted in humans.

3. Human Studies

A. Pharmacokinetics

Varenicline is highly soluble and highly permeable *in vitro* and *in vivo*. Absorption of varenicline is virtually complete after oral administration and systemic availability is high. Maximum plasma concentrations of varenicline occur typically about 3-hours after oral dosing (1–6 hours). Following administration of multiple oral doses of varenicline, steady-state conditions are reached within 4 days. Varenicline exhibits linear kinetics when given as single or repeated doses over the 0.3-mg to 3.0-mg range. Plasma protein binding of varenicline is low (10%-20%). Varenicline is primarily eliminated in the urine as unchanged drug with an elimination half-life of approximately 20 hours. Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine.

B. Abuse Liability Assessment Study

Protocol A3051039, a human laboratory abuse liability study, was conducted in smoking and non-smoking subjects with recreational stimulant experience. CSS pointed out that overall study design was adequate. Because of usual wide confidence intervals in these studies and relatively small N's, CSS advised that individual subjects' response data, along with mean data, will be reviewed. CSS noted also that the choice of comparator, amphetamine, only allows for conclusions regarding varenicline in relation to a C-II drug. CSS advised that an additional arm be added to the study, to comparison with a C-IV stimulant, such as phentermine (C-IV). The additional arm was not included, however.

Results: In individuals who both smoked cigarettes and used stimulants, 1-mg varenicline did not produce statistically significant increases in positive or negative subjective measures. In the non-smoking population, a single oral dose of 1-mg varenicline produced average increases in subjective responses for "good drug effects" and "high" that were statistically significantly greater than placebo, but less than those responses produced on the same scales by a single oral dose of amphetamine at either 15 mg or 30 mg. Only two of 20 subjects responded greater to 1 mg varenicline than either dose of amphetamine to increased drug liking; 90% of the non-smokers responded to 1 mg as they did to placebo. Varenicline (1 mg) produced statistically significantly greater increases in subject-rated "nausea" compared to placebo; neither amphetamine dose did. Amphetamine (15 and 30 mg) produced statistically significant increases in positive and negative subjective responses in both subject populations. A 3 mg dose of varenicline uniformly produced unpleasant subjective responses in subjects with a history of stimulant abuse, regardless of cigarette smoking history.

C. Relationship of Abuse Liability to CNS Adverse Events

The pivotal Phase 3 Studies provided evidence of varenicline (1 mg BID) efficacy as an aid to smoking cessation, and superiority to Zyban.

The most commonly reported TEAEs during the Phase-2/3 studies were predominately GI and psychiatric/neurologic. Overall, adverse event data showed that varenicline is commonly associated with nausea, insomnia, abnormal dreams and other sleep disturbances, and headache. Nausea, by far the most common adverse event, was dose-related, occurring in 30% to 40% of patients, depending on dose and treatment duration. Insomnia, abnormal dreams and other sleep disturbances were also dose-related.

From clinical trials, frequency of occurrence of adverse events are defined as follows: "frequent" is occurring in at least 1/100 patients; "infrequent" is occurring in <1/100 to 1/1000 patients; and "rare" is occurring in fewer than 1/1000 patients.

Frequent *Nervous System Disorders* include Disturbance in attention, Dizziness, Sensory disturbance, and Somnolence. Infrequent and rare events include Amnesia, Lethargy,

Psychomotor hyperactivity, Balance disorder, Mental impairment, Psychomotor skills impaired, Transient ischemic attack.

Psychiatric Disorders include Mood swings (infrequent) and Thinking abnormal, Euphoric mood, and Hallucination which are rare terms.

Under *Gastrointestinal Disorders*, frequent events include Abdominal distension and pain, Diarrhoea, and Gastroesophageal reflux disease.

Withdrawal: There were no clinical studies conducted to specifically evaluate withdrawal effects following varenicline discontinuation. However, several AE's occurred with higher frequency in the initial 7-day post-treatment period in varenicline-treated than in placebo-treated patients: 'Irritability' (3.6% vs. 0.2%); 'Nicotine dependence' (3.1% vs. 0%), 'Sleep disorders and disturbances' (2.85 and 0.2%); 'Headache' and 'Dizziness' (each $\approx 1\%$ vs. 0% in placebo).

Overdose Experience: Two cases of intentional varenicline overdose were reported during Phase 2/3. Intentional dose escalation does not appear to have occurred.

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/s/

Michael Klein
5/8/2006 04:28:57 PM
CHEMIST

Deborah Leiderman
5/8/2006 06:05:24 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: May 8, 2006

TO: Bob Rappaport, M.D., Acting Director
Division of Anesthesia, Analgesia, and Rheumatology Products

VIA: Dominic Chiapperino, Ph.D., Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Patient Labeling for Chantix (varenicline tartrate), Tablets, NDA 21-928

Background and Summary

The following is our suggested revised patient labeling for Chantix (varenicline tartrate), Tablets, NDA 21-928. We have made it consistent with the PI, and removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications). We have put this PPI in the patient-friendly format that we are recommending for all patient information, although, this format is not required for voluntary PPIs. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

The PPI revisions are based on review division revisions to the draft labeling submitted by the sponsor on November 10, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments and Recommendations

We recommend that DDMAC review the PPI from a promotional aspect because the PPI appeared quite promotional in tone and PPIs can be used in lieu of the brief summary in DTC ads. We removed some promotional statements but that is not the area of our expertise.

Comments to the review division are bolded, underlined and italicized. We can provide revised documents (marked and clean) in Word if requested by the review division. Please call us if you have any questions.

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/s/

Jeanine Best
5/8/2006 05:04:51 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
5/8/2006 05:07:27 PM
DRUG SAFETY OFFICE REVIEWER

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Folkendt, Michael M

From: Garcia, Thomas P [thomas.p.garcia@pfizer.com]
Sent: Wednesday, May 03, 2006 4:33 PM
To: Harapanhalli, Ravi S; Folkendt, Michael M
Cc: Bertha, Amy; Nosal, Roger; Page, Mike; Beaulieu, Dorothy D
Subject: Request for Updated 3.2.P.3.5 Section

Attachments: emfinfo.txt



emfinfo.txt (561 B)

Michael/Ravi

Thank-you for taking the time to speak with Roger and I this afternoon. Per our conversation, the text below is our response to the question below. We will follow this e-mail up with a formal response to this query within the next week. Let me know if you have any questions.

Thank-you.
Tom

3.2.P.3.5. Process Validation and/or Evaluation

The process utilized for this drug product is standard in the industry and utilizes conventional manufacturing techniques and equipment. The commercial process has been successfully validated utilizing a conventional process validation protocol that was applied during the manufacture of three 0.5 mg batches and one 1 mg batch of varenicline tablets.

-----Original Message-----

From: Harapanhalli, Ravi S [mailto:ravi.harapanhalli@fda.hhs.gov]
Sent: Tuesday, May 02, 2006 6:21 PM
To: Garcia, Thomas P
Cc: Harapanhalli, Ravi S; Bertha, Amy
Subject: RE: Commercial Batch Stratified Core Data

Tom,

Another loose end to be fixed. Could you please provide updated section P.3.5 (Process validation) to the NDA with a summary data from the completed process validation studies? Alternatively, provide a response indicating that the process validation has been completed and that section P.3.5 would be updated by certain specified date.
Thanks

Ravi S. Harapanhalli, Ph.D.
Chief, CMC Branch V (Pre-marketing)
(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and Oncology Products)
Division III, ONDQA
Center for Drug Evaluation and Research, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

-----Original Message-----

From: Garcia, Thomas P [mailto:thomas.p.garcia@pfizer.com]
Sent: Tuesday, May 02, 2006 4:49 PM
To: Folkendt, Michael M
Cc: Harapanhalli, Ravi S; Beaulieu, Dorothy D; Page, Mike; Nosal, Roger; Bertha, Amy
Subject: RE: Commercial Batch Stratified Core Data

Michael

The following text contains Pfizer's response to the question below.

Question 305Q035 (Received 02-MAY-2006):

a) Regarding the response to 305Q026, the text indicates that a limit will be established for [] and [] at [] max. Please clarify the limit for [] which is listed as NMT [] in Figure 3.2.S.2.4-11.

Pfizer Reply: The response provided in 305Q026 is correct, and a limit of NMT [] will be established for [] and []. The value reported under Figure 3.2.S.2.4-11 (NMT []) will be corrected to NMT [] and a revised figure will be provided in Section S.2.4. Pfizer apologizes for any confusion this discrepancy may have caused.

b) If section S.2.4 is also being revised, correct a possible typo in the text below Fig 3.2.S.2.4-13: "range of [] percent).

Pfizer Reply: Pfizer thanks FDA for pointing out this typographical error. The text should be [] as noted in your comment. Pfizer will update Section S.2.4 and correct the text below Fig 3.2.S.2.4-13 to include the proper units.

Please let me know if you have any further questions.

Regards,
Tom

-----Original Message-----

From: Harapanhalli, Ravi S [mailto:ravi.harapanhalli@fda.hhs.gov]
Sent: Tuesday, May 02, 2006 2:49 PM
To: Garcia, Thomas P
Cc: am Ende, Mary T; Harapanhalli, Ravi S
Subject: RE: Commercial Batch Stratified Core Data
Importance: High

Hi Tom,

Since Amy is on leave and since we are finalizing the reviews, I am sending a clarification question with reference to Pfizer's responses we received last Friday. Please have some one respond to this immediately, preferably by COB today.

Question:

Regarding the response to 305Q026, the text indicates that a limit will be established for [] at [] max. Please clarify the limit for [] which is listed as NMT [] in Figure 3.2.S.2.4-11.

If section S.2.4 is also being revised, correct a possible typo in the text below Fig 3.2.S.2.4-13: "range of [] ppm" : []

percent)

Thanks

Ravi S. Harapanhalli, Ph.D.
Chief, CMC Branch V (Pre-marketing)
(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and
Oncology Products)
Division III, ONDQA
Center for Drug Evaluation and Research, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

-----Original Message-----

From: Garcia, Thomas P [mailto:thomas.p.garcia@pfizer.com]
Sent: Wednesday, April 26, 2006 2:54 PM
To: Harapanhalli, Ravi S
Cc: am Ende, Mary T
Subject: Commercial Batch Stratified Core Data

Ravi

Mary and I would like to discuss [] contained in the
attached file during this afternoon's teleconference as part of a
proposed response to Query #6. The data is from stratified samples of
tablet cores for the ~ batches of tablets manufactured thus far for the
launch campaign. We apologize for not being able to get this to you
sooner and understand if you need more time to digest it.

Regards,
Tom

> > <<Query 6 - Stratified Core Results Update_~ batches.doc>>
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annotations on 04/26/2006 02:54:04 PM

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/s/

Michael Folkendt
5/9/2006 04:38:43 PM
PROJECT MANAGER FOR QUALITY

Ravi Harapanhalli
5/9/2006 06:39:12 PM
CHEMIST

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-928

4-24-06

Pfizer Inc
Attention: Mike Page, Director
50 Pequot Ave
New London, CT 06320

Dear Mr. Page:

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

We also refer to the teleconference between representatives of your firm and the FDA on March 14, 2006. The purpose of the meeting was to discuss the questions outlined in the IR letter dated March 13, 2006.

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

If you have any questions, call me, at (301) 796-1647.

Sincerely,

(See appended electronic signature page)

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

TELECONFERENCE DATE: March 14, 2006
TIME: 3:00 pm- 4:00 pm
APPLICATION: NDA 21-928
DRUG NAME: Varenicline tartrate tablets
MEETING CHAIR: Chi-wan Chen
MEETING RECORDER: Amy Bertha

APR 24 2006

FDA ATTENDEES:

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Chi-wan Chen, Deputy Directory
Ravi Harapanhalli, Branch Chief, Division of Pre-Marketing Assessment III
Ying Wang, Review Chemist, Manufacturing Sciences Branch
Steve Miller, Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment II
Amy Bertha, Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Roger Nosal, Executive Director, Global Regulatory CMC
Tom Garcia, Associate Director, Global Regulatory CMC
Tom Hutchinson, Senior Director, Global Manufacturing Compliance
Frank Busch, Research Fellow, Development API
Mary am Ende, Associate Research Fellow, Solids & PE Development
Tim Graul, Senior Principal Scientist, Development Analytical
Mike Page, Director, Worldwide Regulatory Affairs
Charlie Santa Maria, Associate Director, Development API
Shaileen English, Scientist, Development Analytical
Rob Timpano, Senior Scientist, Development Analytical
Dot Beaulieu, Principal Scientist, Global Regulatory CMC
Stephane Caron, Director, Development API

BACKGROUND:

Varenicline tartrate [] NDA 21-928 was submitted to the FDA on November 10, 2005. This teleconference was mutually agreed [] and is intended as a follow up to the March 13, 2006 IR letter. The purpose of the meeting was to provide the opportunity to clarify the items in the IR letter.

THE MEETING:

During the teleconference FDA and Pfizer discussed the questions outlined in the March 13, 2006 IR letter. Specifically, []

] process. However, no agreement was reached on how information [] would be incorporated into the NDA, and whether they would be part of the agreement for post-approval change.

[

]

[

]

[]

There were no additional requests, agreements or decisions made in the meeting. Pfizer will provide their official answer to the IR letter in the form of an NDA amendment.

Minutes Preparer: Amy Bertha

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment

Chair Concurrence: Chi-wan Chen

Chi-wan Chen
Deputy Director
Office of New Drug Quality Assessment

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/s/

Amy Bertha

4/27/2006 11:25:36 AM

ADRA Rev #1 of Action Package for NDA 21-928

Reviewer: Lee Ripper, HFD-102

Date received: 4/21/06

Date of review: 4/28/06

Date original NDA received: 11/10/05

UF goal date: 5/10/06

Proposed Indication: Smoking cessation

Action type: AP

RPM: Dominic Chiapperino

Drug Classification: 1P

505(b)(1) application

Patent Info on form FDA 3542a: Yes

Debarment Certification: Yes, AC

Financial Disclosure: Several investigators had significant SPOOS or equity interests.

Addressed in MO Safety rev, section 4.6.

Safety Update: Recd 2/10/06, MO Safety rev, section 4.1 lists as a data source

Risk Management Plan: ODS concluded a RMP is not warranted

Clinical Inspection Summary: 4/19/06, data appear to be AC. Discussed in MO Safety rev, section 4.4.1.

ODS/DMETS Review of Proprietary Name: 4/26/06, no objections to proprietary name, Chantix

DSRCS Review of PPI: 5/8/06

DDMAC Review: No review

EA: Categorical exclusion claimed

EER: AC 4/7/06

PSC/WU Mtg: 4/6/06

CMC section to Rick Lostritto, 5/1/06. Tertiary review was done by Chi-Wan Chen, Deputy Director, ONDQA, because the application J
P/T section to Ken Hastings, 5/1/06. No comments.

1. Exclusivity Summary and Pediatric Page need to be completed.

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/s/

Leah Ripper
5/10/2006 05:48:49 PM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

4/21/06

NDA 21-928

INFORMATION REQUEST LETTER

Pfizer Inc
Attention: Mike Page, Director
50 Pequot Ave
New London, CT 06320

Dear Mr. Page:

Please refer to your November 9, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Champix™ (varenicline tartrate) tablets.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests:

1. [

]

2. [

1

]

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7. During the past two discussions on this NDA, it was agreed that [

]

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

Sincerely,

(See appended electronic signature page)

Chi-wan Chen, Ph.D.
Deputy Director
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Chi Wan Chen

4/21/2006 04:11:42 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Nancy A. Rigotti, M.D.
Massachusetts General Hospital Tobacco Research and Treatment Center
50 Staniford Street, 9th Floor
Boston, Massachusetts 02114

4/17/06

Dear Dr. Rigotti:

Between March 16 and 30, 2006, Ms. Michelle M. Noe, representing the Food and Drug Administration (FDA), conducted an inspection and met with you to review your conduct of a clinical investigation (protocol A3051036 entitled "A Twelve-Week, Double-blind, Placebo-Controlled, Randomized, Multicenter Study with Follow-up Evaluating the Safety and Efficacy of Varenicline Tartrate [CP-526,555] in Comparison to Zyban for Smoking Cessation") of the investigational drug varenicline (Champix), performed for Pfizer, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Noe during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{ See appended electronic signature page }

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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/s/

Constance Lewin
4/17/2006 12:30:19 PM

NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA # 21-928

Supplement #

Efficacy Supplement Type SE-

Trade Name: Champix

Established Name: Varenicline tartrate

Strengths: 0.5mg, 1.0 mg oral tablets

Applicant: Pfizer, Inc.

Agent for Applicant: Michael J. Page, B.Sc., Director

Date of Application: November 9, 2005

Date of Receipt: November 10, 2005

Date of Filing Meeting: December 15, 2005

Filing Date: January 9, 2006

Action Goal Date (optional): May 10, 2006

User Fee Goal Date: May 10, 2006

Indication(s) requested: Smoking Cessation

Type of Original NDA:

(b)(1) ☒(b)(2) ☐

OR

Type of Supplement:

(b)(1) ☐(b)(2) ☐**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application

OR

☐ NDA is a (b)(2) application

Therapeutic Classification:

S ☐P ☒

Resubmission after withdrawal?

☐

Resubmission after refuse to file?

☐

Chemical Classification: (1,2,3 etc.)

1

Other (orphan, OTC, etc.)

N/A

Form 3397 (User Fee Cover Sheet) submitted:

YES ☒NO ☐

User Fee Status:

Paid ☒

Exempt (orphan, government)

☐

Waived (e.g., small business, public health)

☐

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐
- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
- Was form 356h included with an authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A ☒ YES ☐ NO ☐
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐
- Is it an electronic CTD (eCTD)? N/A ☐ YES ☒ NO ☐
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, 5 Years NO ☐
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐
- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: INDs 58,994 and 59,000
- End-of-Phase 2 Meeting(s)? Date(s) December 9, 2002, and October 9, 2003 NO ☐
(CMC EOP2)
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) June 9, 2005, and August 18, 2005 NO ☐
(CSS/Abuse liability)
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES ☒ NO ☐
- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A ☐ YES ☒ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐
- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES ☒ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

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ATTACHMENT

MEMO OF FILING MEETING

DATE: December 15, 2005

BACKGROUND: Varenicline tartrate is a new molecular entity developed for smoking cessation. It is claimed to be an improvement on currently marketed drugs for this indication, and a comparative claim is made of superiority to Zyban® (bupropion hydrochloride). On the basis of initial inspection of clinical study results which appear to demonstrate superiority over Zyban®, the Division will grant priority review status to NDA 21-928.

ATTENDEES:

Curtis Rosebraugh, M.D., Deputy Director, Office of Drug Evaluation II
Bob A. Rappaport, M.D., Director, Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Rigoberto Roca, M.D., Deputy Director, DAARP
Celia Winchell, M.D., Medical Team Leader, Addiction Products, DAARP
Howard Josefberg, M.D., Medical Officer, DAARP
Dan Mellon, Ph.D., Supervisor, Pharmacology/Toxicology, DAARP
Mamata De, Ph.D., Pharmacology/Toxicology Reviewer, DAARP
Dominic Chiapperino, Ph.D., Regulatory Project Manager, DAARP
Thomas J. Permutt, Ph.D., Team Leader, Statistics, Division of Biometrics II (DB2)
Joan Buenconsejo, Ph.D., Statistics Reviewer, DB2
Suresh Doddapaneni, Ph.D., Team Leader, Division of Clinical Pharmacology and Biopharmaceutics 2 (DCPB2)
Srikanth Nallani, Ph.D., DCPB2
Stephen Miller, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment II
Ying Wang, Ph.D., Chemist, Division of Manufacturing Sciences
Ravi Harapanhalli, Ph.D., Branch Chief, Division of Pre-Marketing Assessment III
Amy Bertha, Regulatory Health Project Manager,

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline

Medical:
Secondary Medical:
Statistical:
Pharmacology:
Statistical Pharmacology:
Chemistry:

Reviewer

Howard Josefberg, M.D.
Celia Winchell, M.D.
Joan Buenconsejo, Ph.D.
Mamata De, Ph.D.
N/A
Stephen Miller, Ph.D. (drug substance); Ying Wang, Ph.D. (drug product); Amy Bertha (Project Manager), Ali Al Hakim, Ph.D. (Pharmaceutical Assessment Lead)

Environmental Assessment (if needed):
Biopharmaceutical:
Microbiology, sterility:
Microbiology, clinical (for antimicrobial products only): N/A

DSI:
Regulatory Project Management:
Other Consults:

Carolanne Currier
Dominic Chiapperino, Ph.D.
ODS, DDMAC, DMETS, CSS

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐

If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

• Clinical site inspection needed? YES ☒ NO ☐

• Advisory Committee Meeting needed? YES, date if known _____ NO ☒

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

• Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

• GLP inspection needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

• Establishment(s) ready for inspection? YES ☒ NO ☐
• Microbiology YES ☐ NO ☒

ELECTRONIC SUBMISSION:

Any comments: The applications was submitted in eCTD format, and appears to have appropriate well-functioning links.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- ☐ The application is unsuitable for filing. Explain why:
- ☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

No specific issues identified for 74-day filing letter.

Dominic Chiapperino, Ph.D.
Regulatory Project Manager, HFD-170

Appendix A to NDA Regulatory Filing Review

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) 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.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES ☐ NO ☐

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES ☐ NO ☐

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, YES ☐ NO ☐
ORP?

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under YES ☐ NO ☐
section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs
(see 21 CFR 314.101(d)(9)).

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made YES ☐ NO ☐
available to the site of action less than that of the reference listed drug (RLD)?
(See 314.54(b)(1)). If yes, the application should be refused for filing under
21 CFR 314.101(d)(9)).

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise YES ☐ NO ☐
made available to the site of action unintentionally less than that of the RLD (see
21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under
21 CFR 314.101(d)(9)).

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and
identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.
(Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

- ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

- ☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.
- ☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- ☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES ☐ NO ☐
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES ☐ NO ☐
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A ☐ YES ☐ NO ☐
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?
N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES ☐ NO ☐

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# _____ NO ☐

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ☐ NO ☐

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

/s/

Dominic Chiapperino
4/13/2006 11:18:12 AM
CSO



Global Research & Development

11 April, 2006

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
c/o Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

THIS DOCUMENT CONTAINS CONFIDENTIAL AND/OR
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BE DISCLOSED OR USED, IN WHOLE OR IN PART, FOR ANY
OTHER PURPOSE WITHOUT THE PRIOR WRITTEN CONSENT
OF PFIZER INC.

Re: NDA 21-928 (varenicline tartrate) Tablets
Amendment to Pending NDA – Submission of Revised Package Labeling to Reflect Change
in Tradename

Dear Dr Rappaport:

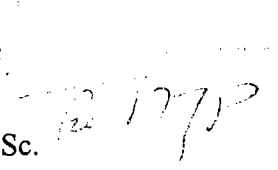
Please refer to above referenced pending NDA. Enclosed please find revised package labeling to reflect the recent change in tradename for varenicline tartrate from CHAMPIX to CHANTIX.

The revised packaging labeling includes Trade and Professional Sample artwork for heat seal cards and monthly display cartons. Included also are two Trade bottle labels as well as one Professional Sample Early Experience Kit display carton.

The CD-Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 9 MB in size.

Should you have any questions regarding this submission, please contact either me at (860) 715 1110 (phone) or (860) 686 2599 (fax) or Samantha McNamara at (212) 573-2241 (office phone).

Sincerely,


Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS

**DIVISION DIRECTOR SUMMARY REVIEW AND BASIS FOR APPROVAL
RECOMMENDATION**

DATE: April 8, 2006

DRUG: Chantix (varenicline,

NDA: 21-928

NDA Code: Type 1P

SPONSOR: Pfizer, Inc.

INDICATION: For smoking cessation

Pfizer, Inc. submitted NDA 21-928 in support of marketing approval for Chantix (varenicline, 0.5-mg and 1-mg tablets) on November 10, 2005. The application was granted a priority review based on the finding that the studies, on face, appeared to demonstrate a clinically important improvement in efficacy compared to all of the currently available treatments for smoking cessation.

Review of the CMC portion of this application was completed by Stephen Miller, Ph.D and Ying Wang, Ph.D. Review of the pharmacology and toxicology data was completed by Mamata De, Ph.D. Review of the clinical pharmacology and biopharmaceutics data was completed by Srikanth Nallani, Ph.D. A statistical review was completed by Joan Buenconsejo, Ph.D. A clinical safety review was completed by Howard Josefberg, M.D. and a review of the efficacy data was completed by Celia Jaffe Winchell, M.D. Dr. Winchell also provided a secondary review of the safety data and an overall risk benefit analysis based on the entirety of the application. Consultation on this application was also obtained from the Division of Drug Marketing, Advertising and Communications (DDMAC), the Controlled Substances Staff (CSS), the Study Endpoints and Labeling Development Team (SEALD) and the Office of Drug Safety (ODS).

Varenicline is a selective, partial agonist of the $\alpha 4\beta 2$ nicotinic receptor subtype. Based on animal models, a partial agonist at this receptor subtype would be expected to provide relief from nicotine craving and withdrawal symptoms and, in addition, interfere with the action of full agonists such as nicotine to reduce the psychogenic rewards associated with smoking. The sponsor included an active-treatment arm in its Phase 2 studies to establish assay sensitivity. Based on preliminary results that indicated that varenicline might be more effective than Zyban (bupropion HCl), Pfizer decided to pursue a superiority claim by incorporating a Zyban arm into its Phase 3 trials. The on-face results of these trials were the basis for the Division's decision to grant the priority review.

Efficacy:

The sponsor submitted six adequate and well-controlled trials in support of efficacy. As per Dr. Winchell's review (pages 16 and 17), the smoking cessation trials were all of similar design. Subjects were randomized to placebo, Chantix (various doses in Phase 2 and 1 mg bid in Phase 3) and, in three studies, Zyban at the labeled dosing regimen of 150 mg bid after initial dose titration. Subjects were to quit smoking on Day 7. Smoking status was assessed at each study visit via self-report and exhaled CO. Subjects received an educational booklet on smoking cessation and were provided with up to 10 minutes of counseling at each visit following AHRQ guidelines. Subjects who completed the 12-week treatment period were then followed for an additional 40 weeks.

The primary outcome measure was the 4-Week Continuous Quit Rate (CQR) for the last four weeks of treatment, Weeks 9 through 12 for most of the studies. The responder definition required that a subject be completely abstinent for the last 4 weeks of treatment and have end-expiratory exhaled CO measurements of less than or equal to 10 ppm. An additional analysis of importance to the Division was the proportion of subjects who initiated abstinence by Week 3 and then maintained that abstinence throughout the treatment period. This analysis was consistent with the Division's current analytic approach used to assess other nicotine agonist products.

The secondary outcome measures included:

- Continuous Abstinence Rate from Week 9 through Week 52
- Long-term Quit Rate through Week 52 defined as the proportion of subjects who have successfully quit during the treatment phase based on the 4-Week CQR from Week 9 through Week 12 and who have had no more than 6 days of smoking during the non-treatment phase
- Continuous Abstinence Rate from Week 9 through Week 24
- 7-day point-prevalence of smoking cessation at Weeks 12, 24 and 52

- 4-week point-prevalence of smoking cessation at Week 52
- Change from baseline in body weight
- Results of the Minnesota Nicotine Withdrawal Scale, the Brief Questionnaire of Smoking Urges, and the Smoking Effects Inventory

The Maintenance of Efficacy study (A3051035) enrolled subjects into a 12-week, open-label phase during which they were treated with Chantix 1 mg bid after an initial titration from 0.5 mg qd over a week. At Week 12, subjects who had been abstinent for the previous 7 days were re-randomized to blinded treatment with either the same dose of Chantix or placebo for an additional 12 weeks. The primary outcome variable was the Continuous Abstinence Rate for Weeks 13 through 24.

Secondary endpoints included:

- Continuous Abstinence Rate for Weeks 13 through 52
- Long-term Quit Rate at Week 52
- 7-day point-prevalence of abstinence
- 4-week point-prevalence of anstinence
- Time to first cigarette after randomization

Results:

Studies A3051028 (1028) and A3051036 (1036)

Dr. Buenconsejo analyzed the abstinence rates using the more conservative imputation methodology that the sponsor had employed in their Phase 2 studies, and calculated rates employing shorter grace periods than the protocol-specified 8 weeks. These re-analyses did not change the overall efficacy results. Dr. Winchell's summary table (page 20 of her review) is reproduced below. It includes the results of the primary efficacy analyses performed by both the sponsor and Dr. Buenconsejo.

Primary Efficacy Criterion - Four-Week Abstinence Rates

	Study A1028			Study A1036		
	Varenicline	Placebo	Zyban	Varenicline	Placebo	Zyban
Applicant's results:						
ITT Subjects	N=349	N=344	N=329	N=343	N=340	N=340
Abstinent (%)	155 (44%)	61 (18%)	97 (30%)	151 (44%)	60 (18%)	102 (30%)
Odds ratio		3.9	2.0		3.8	1.9
(varenicline vs.)		(2.7, 5.6)	(1.4, 2.7)		(2.7, 5.5)	(1.4, 2.6)
p-value		<0.0001	<0.0001		<0.0001	<0.0001
(varenicline vs.)						
Evaluable	N=309	N=302	N=275	N=310	N=304	N=295
Abstinent (%)	152 (49%)	61 (20%)	96 (35%)	151 (49%)	60 (20%)	99 (34%)
Odds ratio		4.1	1.9		4.1	1.9
(varenicline vs.)		(2.9, 6.0)	(1.3, 2.6)		(2.8, 5.8)	(1.4, 2.7)
p-value		<0.0001	0.0004		<0.0001	0.0001
(varenicline vs.)						
Reviewer's results:						
ITT Subjects	N=349	N=344	N=329	N=343	N=340	N=340
Abstinent (%)	152 (44%)	60 (17%)	97 (30%)	150 (44%)	60 (18%)	101 (30%)
Odds ratio		3.9	1.9		3.8	1.9
(varenicline vs.)		(2.7, 5.5)	(1.4, 2.6)		(2.7, 5.4)	(1.4, 2.6)
p-value (varenicline vs.)		<0.0001	0.0001		<0.0001	0.0001

The sponsor's and Dr. Buenconsejo's analyses of the long-term abstinence rates in these studies documented that more subjects treated with Chantix remained abstinent at 40 weeks compared to subjects treated with placebo. (See Dr. Winchell's table on page 22 of her review.)

While the secondary outcome measures were generally supportive of the primary outcome measure results, the subjective measures were less consistently supportive. In addition, the sponsor used unacceptable methodologies in evaluating some of these Patient Reported Outcomes such as selecting unvalidated subscales for analysis. Nevertheless, based on the review and assessment provided by the SEALD team, Dr. Winchell has concluded that the sponsor has adequately demonstrated evidence of a treatment effect for reducing "urge to smoke," and that that claim could be represented in the product labeling.

Studies A3051007 (1007) and A3051006 (1006)

These Phase 2 studies were designed to assess dosing regimens and have been reviewed in detail by Dr. Winchell (see pages 26 through 35 of her review). It is important to note, however, that while early studies suggested that the maximum tolerated daily dosage was

2 mg, the incidence of nausea and vomiting was lower when the dose was administered as 1 mg bid rather than as a single, daily-dose of 2 mg; and that Study 1006 demonstrated that a flexible dosing strategy within the range of 0.5 mg to 2 mg per day allowed for increased tolerability while maintaining efficacy. Indeed Study 1006 suggested that, given the opportunity to self-titrate, most smokers would not choose the dose proposed by Pfizer for marketing, 1 mg bid. The results of Study 1007 also served as the basis for the initial titration phase employed in the Phase 3 studies.

These findings led the review team to question whether the sponsor's dosing recommendation for 1 mg bid was too high for most patients. This matter was discussed with the sponsor in a teleconference and they suggested that, for smokers, the most essential feature of a drug intervention should be that it will provide an important opportunity for quitting. Therefore, they argued that it is essential that patients be treated initially with the high dose in order to provide them with this opportunity, especially in light of the relatively benign nature of the primary toxicity, nausea. They did agree to include labeling that would allow prescribers to decrease the dose for patients who are unable to tolerate the treatment even with encouragement by their healthcare providers. Documentation of the effect size issue and explication of the sponsor's rationale for not lowering the recommended starting dose was submitted to the Division. After review of this documentation and the sponsor's arguments as defined during the teleconference, the review team concluded that the sponsor's position is sound and that their suggested dosing regimen is reasonable.

Study A3051002 (1002)

This study was briefly summarized by Dr. Winchell (on pages 42 through 44 of her review) as it was the sponsor's initial Phase 2 study and the primary outcome measure ("any four-week period of abstinence") was not acceptable based on current Agency standards for smoking cessation trials. However, it is of note that additional analyses of the data that looked at more acceptable outcome variables ("CQR calculated for Weeks 3 through 6 and Weeks 4 through 7") did find a statistically significant treatment effect for Chantix at both the sponsor's proposed dosing regimen of 1 mg bid and at lower doses of 1 mg qd and 0.3 mg qd.

Study A3051035 (1035)

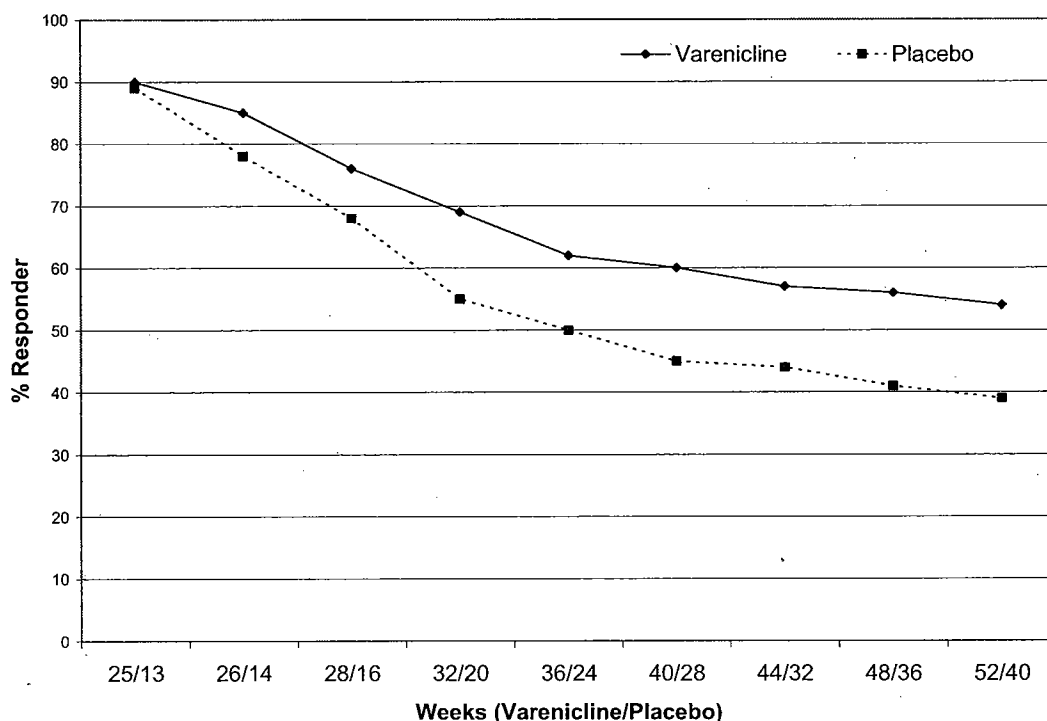
Dr. Buenconsejo also reanalyzed the data from this study using the more conservative imputation methodology. The sponsor's and Dr. Buenconsejo's analyses are summarized in Dr. Winchell's table on page 38 of her review, reproduced below:

Appears This Way
On Original

	Pfizer's analysis		Reviewer Re-analysis	
	Double-Blind Varenicline	Double-Blind Placebo	Double-Blind Varenicline	Double-Blind Placebo
Continuous Abstinence, Weeks 13-24				
ITT Subjects	N=601	N=603	N=601	N=603
Abstinent (%)	425 (71%)	301 (50%)	420 (70%)	301 (50%)
Odds ratio (95% CI) vs. placebo		2.5 (2.0, 3.2)		2.4 (1.9, 3.0)
p-value vs. placebo		<0.0001		<0.0001
Evaluable	N=574	N=574	N=574	N=574
Abstinent (%)	418 (73%)	299 (52%)	415 (72%)	299 (52%)
Odds ratio (95% CI) vs. placebo		2.5 (2.0, 3.2)		2.5 (1.9, 3.2)
p-value vs. placebo		<0.0001		<0.0001
Continuous Abstinence, Weeks 13-53				
ITT Subjects	N=601	N=603	N=601	N=603
Abstinent (%)	265 (44%)	224 (37%)	247 (41%)	214 (35%)
Odds ratio (95% CI) vs. placebo		1.3 (1.1, 1.7)		1.3 (1.0, 1.6)
p-value vs. placebo		0.0123		0.0394
Evaluable	N=574	N=574	N=574	N=574
Abstinent (%)	262 (46%)	223 (39%)	244 (43%)	214 (37%)
Odds ratio (95% CI) vs. placebo		1.3 (1.0, 1.7)		1.3 (1.0, 1.6)
p-value vs. placebo		0.0193		0.0705

Dr. Buenconsejo also graphed the proportion of subjects who were abstinent during the last week of Chantix treatment (Week 12 for the placebo group and Week 24 for the Chantix group). This analysis attempts to accurately compare whether 6 months of Chantix treatment is superior to 3 months of Chantix treatment, the initial treatment exposures to Chantix for the Chantix and placebo groups, respectively. Her graph is reproduced below from page 40 of Dr. Winchell's review.

Continuous Abstinence Rate from Week 13/25 to Week 40/52



On page 40 of her review, Dr. Winchell concludes:

Although both groups show that the first three months after treatment discontinuation are a time when smokers are vulnerable to relapse, the relapse curve for those who had a longer period of varenicline treatment is shallower.

Clinical Safety:

There were 4690 subjects exposed to Chantix in the sponsor's safety database. Of those subjects, 456 were treated with the highest proposed dose, 1 mg bid for at least 24 weeks, 112 of those subjects for 364 days or more. There were five deaths reported in the safety database, three in Chantix-treated subjects, and one each in Zyban and placebo-treated subjects. One death on blinded therapy was added at the time of the safety update. The review team has determined that none of these deaths was clearly associated with Chantix exposure.

Serious adverse events occurred with similar frequencies in the Chantix, Zyban and placebo groups. The most frequent adverse events leading to discontinuation were: nausea, headache and insomnia. The incidence of nausea leading to discontinuation in the Chantix population was clearly dose related (this has been documented in Dr. Zheng's

pharmacometric analysis), and occurred overall in ~3% of these subjects. Nausea leading to discontinuation also occurred with greater frequency in the Chantix group compared to either the Zyban or placebo groups. Headache leading to discontinuation occurred with similar frequency in the three treatment groups; insomnia leading to discontinuation occurred most frequently in the Zyban group and with equal frequency in the Chantix and placebo groups.

Based on an apparent increase in cardiac events in the Chantix treatment group, and on Dr. Josefberg's analysis of these data, Dr. Winchell completed a detailed and thorough analysis of the serious cardiac (both ischemic and arrhythmic) adverse events. This analysis is described in her review and documents that there was no increase in these events in the Chantix-treated subjects.

Nausea was reported in as many as 40% of the Chantix-treated subjects. Dose titration appeared to be beneficial in reducing the proportion of subjects who experienced nausea. While weight gain occurred more frequently in Chantix-treated compared to placebo-treated subjects, it was clearly correlated with smoking status. As expected, those subjects who were able to remain abstinent also had a greater risk of gaining weight. The most frequent adverse events in the Chantix-treated subjects were: nausea, vomiting, flatulence, constipation, insomnia, abnormal dreams, dysgeusia and increased appetite.

Nonclinical Safety, Clinical Pharmacology and Biopharmaceutics; Chemistry, Manufacturing and Controls:

The review teams for these disciplines have determined that there are no issues of concern which would impact on the approvability of this application.

Abuse Liability:

The Controlled Substances Staff has determined that the preclinical and clinical abuse liability data demonstrate that this product is not likely to have an abuse risk.

Discussion:

I concur with Dr. Winchell's conclusions and recommendation that this product may be approved. While there is a greater risk of nausea with the sponsor's proposed starting dose of 1 mg bid, there is an incremental increase in effectiveness with this dose. In smokers, the benefits of any increased chance of quitting outweighs this potential risk. In addition, the agreed upon labeling will allow dosage reduction as needed for tolerance.

I also concur with Dr. Winchell that the sponsor has demonstrated that Chantix 1 mg bid is superior to Zyban at its approved dose. Finally, the likelihood of remaining abstinent over the long term does appear to be greater when Chantix is administered for 6 months.

No other clinical, preclinical, abuse liability or product quality concerns have been found by the specific review teams.

Recommended Action:

Approval

Bob A. Rappaport, M.D.

Director

Division of Anesthesia, Analgesia and Rheumatology Products

Office of Drug Evaluation II, CDER, FDA

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

/s/

Bob Rappaport
5/8/2006 09:29:04 PM
MEDICAL OFFICER

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

DATE RECEIVED: Mar. 22, 2006

DESIRED COMPLETION DATE:

ODS CONSULT #:

DATE OF DOCUMENT: Nov. 10, 2005

Apr. 1, 2006

06-0053-1

PDUFA DATE: May 10, 2006

TO: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia and Rheumatology Products
HFD-170

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

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

PRODUCT NAME:

Chantix

(Varenicline Tartrate) Tablets

0.5 mg and 1 mg

SPONSOR: Pfizer

NDA #: 21-928

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Chantix. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
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 finds the proprietary name Chantix acceptable from a promotional perspective.

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 Diane Smith, pre-marketing Project Manager, at 301-796-0538.

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 27, 2006

NDA #: 21-928

NAME OF DRUG: **Chantix**
(Varenicline Tartrate) Tablets
0.5 mg and 1 mg

NDA SPONSOR: Pfizer

I. INTRODUCTION

This consult was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products, for an assessment of the proprietary name "Chantix" regarding potential name confusion with other proprietary or established drug names. The sponsor also submitted a name evaluation conducted by [redacted] in support of the proposed proprietary name Chantix. Container labels, carton and insert labeling were provided for review and comment as well.

PRODUCT INFORMATION

Chantix (Varenicline tartrate) is indicated for smoking cessation. It will be available as 0.5 mg and 1 mg tablets. Initially, the recommended dose of Chantix was 1 mg twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Days 8 – End of treatment:	1 mg twice daily

However, the Division has updated the dosing instructions as follows:

Days 1-3	0.5 mg once daily.
Days 4-7	0.5 mg twice daily
Days 8- End of treatment	1 mg twice daily.

Patients should be treated with Chantix for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment at 1 mg twice daily is recommended to further increase the likelihood of long-term abstinence. [redacted]

The proposed packaging for Chantix will be a pack for the first month of therapy which includes 1 card containing eleven 0.5 mg tablets and 3 cards containing fourteen 1 mg tablets. For continuing months of therapy, a pack will include 4 cards containing fourteen 1 mg tablets. Chantix will also be supplied in bottles of — 0.5 mg tablets) and bottles of 56 (1 mg tablets).

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{i,ii} as well as several FDA databases^{iii,iv} for existing drug names which sound-alike or look-alike to "Chantix" 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^v and Clinical Pharmacology^{vi} were also conducted. The Saegis^{vii} 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. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Chantix. 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 did not have any concerns from a promotional perspective regarding the proposed name, Chantix.
2. The Expert Panel identified four (4) proprietary names that were thought to have potential for confusion with Chantix. These products are listed in Table 1 (see below and page 4), along with the dosage forms available and usual dosage.

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

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Chantix	Varenicline Tartrate Tablets: 0.5 mg and 1 mg	Days 1-3: 0.5 mg once daily. Days 4-7: 0.5 mg twice daily. Days 8 - end of treatment: [redacted] 1 mg twice daily.	
Kantrex	Kanamycin Sulfate Injection 75 mg/2 mL, 500 mg/2 mL, and 1 g/3 mL	IM injection: 15 mg/kg/day into two equally divided doses administered at equally divided intervals (e.g., 7.5 mg/kg every 12 hours). IV administration: The dose should not exceed 15 mg/kg/day. The total dose should be divided into 2-3 equally divided doses.	LA/SA

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

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

ⁱⁱⁱ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 1998-2005, and the electronic online version of the FDA Orange Book.

^{iv} Phonetic and Orthographic Computer Analysis (POCA)

^v WWW location <http://www.uspto.gov>.

^{vi} Clinical Pharmacology, online version available at <http://cpip.gsm.com>

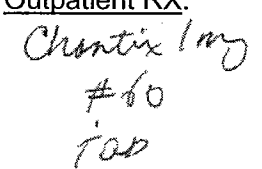
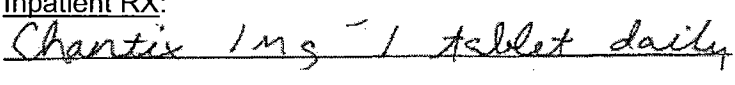
^{vii} Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Chantix	Varenicline Tartrate Tablets: 0.5 mg and 1 mg	Days 1-3: 0.5 mg once daily. Days 4-7: 0.5 mg twice daily. Days 8 - end of treatment: 1 mg twice daily.	
Vantin	Cefpodoxime Proxetil Tablet: 100 mg and 200 mg Granules for oral suspension: 50 mg/5 mL and 100 mg/5 mL	100 mg to 400 mg every 12 hours.	LA
Chenix	Chenodiol Tablet: 250 mg	Dose range is 13-16 mg/kg/day in two divided doses, starting with 250 mg BID for the first 2 weeks and increasing by 250 mg/day each week thereafter.	SA
Centrax	Prazepam Capsule: 5 mg, 10 mg, 20 mg Tablet: 10 mg	10 mg by mouth TID (range 20 - 60 mg per day).	LA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Chantix with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Chantix (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> 	Chantix 1 mg, Dispense #60. Take 1 tablet by mouth once daily.
<u>Inpatient RX:</u> 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT OF PROPRIETARY NAME

In reviewing the proprietary name "Chantix", the primary concerns relating to look-alike and sound-alike confusion with Chantix are Kantrex, Vantin, Chenix, and Centrax.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Chantix.

1. Kantrex was identified to look and sound similar to Chantix. Kantrex is indicated in the short term treatment of serious infections caused by susceptible strains of specific microorganisms. Kantrex is available as an injection for intramuscular or intravenous administration. Kantrex and Chantix may look similar as they both contain seven letters. The letters "-ant-" appear in the middle of the each name. Additionally, the endings can look similar when scripted ("-trex" and "-tix"). Kantrex and Chantix share a phonetic similarity because each name contains two syllables. The first syllable ("Kan-" vs. "Chan-") and the second syllable ("-trex" and "-tix") may sound phonetically similar when spoken. Both names may be orthographically distinguished by the beginning of each name ("K" vs. "Ch"). The upstroke of the letter "h" may help to further distinguish the names. Kantrex and Chantix share an overlapping frequency of administration (twice daily). However, Kantrex and Chantix are differentiated by their indication for use (infections vs. smoking cessation), strength (75 mg/2 mL, 500 mg/2 mL and 1 g/3 mL vs. 0.5 mg and 1 mg), usual dose (7.5 mg/kg vs. 0.5 mg - 1 mg), route of administration (IM or IV vs. oral), and dosage form (injection vs. tablet). Although there is some orthographic resemblance between Kantrex and Chantix, the differentiating product characteristics will help to minimize confusion between the two drug products.

Chantix
Kantrex

2. Vantin was identified to look similar to the proposed name, Chantix. Vantin is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of specific microorganisms. Vantin is available as granules for suspension and as tablets. Vantin and Chantix may look similar since they both share the letters "-ant" and the endings may look similar when scripted ("-in" vs. "-ix"). Although each name begins with a different letter ("V-" vs. "Ch-"), the flow of the letter "C" into the upstroke of the letter "h" may resemble the letter "V" (see example below). Vantin and Chantix overlap in route of administration (oral), frequency of administration (twice daily), and dosage form (tablets). However, Vantin and Chantix have differentiating product characteristics such as indication for use (infections vs. smoking cessation), strength (100 mg, 200 mg, 50 mg/5 mL and 100 mg/5 mL vs. 0.5 mg and 1 mg), and usual dosage (100 mg - 400 mg vs. 0.5 mg - 1 mg). Despite the orthographic similarities and some overlapping product characteristics, DMETS believes the strength, usual dosage and indication for use will help to minimize confusion between Vantin and Chantix.

Chantix
Vantin

3. Chenix was identified to look and sound similar to the proposed name, Chantix. Chenix is indicated to treat gallstones. Chenix and Chantix share a similar beginning and ending that is orthographically and phonetically similar ("Chen-" vs. "Chan-") and ("-ix"). The only differentiating factor is the upstroke of the letter "t" in Chantix. Both drugs share an overlapping frequency of administration (twice daily), route of administration (oral), and dosage form (tablet). However, Chenix and Chantix differ in strength (250 mg vs. 0.5 mg and 1 mg), indication for use (gallstones vs. smoking cessation), and usual dosage (13 -16 mg/kg vs. 0.5 mg - 1 mg). Furthermore, Chenix was discontinued in 1993 and no generic formulations are available. Chenix cannot be found using the following standard common references: Drug Facts and Comparisons, the RedBook, destinationrx.com, rxlist.com, or Walgreens.com. Despite the orthographic and phonetic similarities between Chenix and Chantix, the unavailability of Chenix, lack of generic formulations, strength, and the fact that it no longer appears in standard references will minimize the potential of confusion between the two drugs.

Chenix
Chantix

4. Centrax was identified to look similar to Chantix when scripted. Centrax is indicated as an anti-anxiety agent. Centrax and Chantix begin with the letter "C" and end with the letter "x". Both names contain seven letters. The letters "-ent-" and "-ant-" may look similar when scripted. However, the upstroke of the letter "h" in Chantix and the presence of the letter "r" in Centrax may help to differentiate the names. Centrax and Chantix overlap in route of administration (oral) and dosage form (tablet). However, product differences include indication for use (anxiety vs. smoking cessation), strength (5 mg, 10 mg, 20 mg vs. 0.5 mg and 1 mg), usual dose (20 mg - 60 mg vs. 0.5 mg - 1 mg), and frequency of administration (three times a day vs. twice daily). Additionally, Centrax is discontinued and a generic formulation is not available. Centrax is not available in standard references such as Drug Facts and Comparisons, the RedBook, destinationrx.com, rxlist.com, or Walgreens.com. Despite some orthographic similarities between Centrax and Chantix, the unavailability of Centrax and lack of a generic formulation will help to minimize confusion between the two drugs. Additionally, since Centrax does not appear in standard references, the likelihood of confusion between Centrax and Chantix is further minimized.

Centrax
Chantix

D. . [

] . NAME ANALYSIS

The [] , [] submitted a name evaluation in support of the proposed proprietary name Chantix. [] concluded that Chantix was "a good to excellent name, which would only cause problems if very poorly communicated by prescriber or transcriber". The only name that [] considered to be potentially confusing was Kantrex. DMETS also identified this name and discussed it in section IIC1 of this review. DMETS concurs that Kantrex and Centrax can co-exist in the marketplace with minimal potential for confusion.

7 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Appendix A
Chantix prescription study results

Written Inpatient	Written Outpatient	Verbal
Chantix	Chantix	Chantix
Chantix	Chantix	Chantix
Chantix	Chantix	Shantax
Chantix	Chantix	Shantecks
Chantix	Chantix	Shantix
Chantix	Chantix	Shantix
Chantix	Chantix	Shantix
Chantix	CHANTIX	Shantix
Chantix	Chantix	Shantix
Chantix	Chantix	Shantix
Chantix	Chantix	Shantix
Chantix	Chantix	Shentics
Chantix	Chantix	
Chantix	Chantix	
Chantix	Chantix	
Chantix	Chantix	
Chantrix	Chantix	
	Chontix	
	Chontix	

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/s/

Felicia Duffy
4/26/2006 02:50:22 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/26/2006 03:12:41 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/26/2006 03:23:12 PM
DRUG SAFETY OFFICE REVIEWER

Pfizer Inc
50 Pequot Ave
New London, CT 06320



31 March 2006

Global Research & Development

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
c/o Central Document Room
5901-B Ammendale Road
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New Drug Application 21-928 (varenicline tartrate) Tablets

RE: Response to Request for Information, Updated Table to Include VAS Nausea Scale

Dear Dr Rappaport:

Referring to a telephone communication received from Dominic Chiapperino on March 30, 2006, we enclose a response to the Request for Information regarding an updated table from the March 27, 2006 (correspondence #0017) submission to include VAS Nausea scale.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 620 KB in size.

Should you have any questions regarding this submission, please contact me at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in cursive script, appearing to read "Michael J. Page".

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

MP/js
Deskcopy: Dominic Chiapperino (1 CD)



31 March 2006

Global Research & Development

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
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New Drug Application 21-928 (varenicline tartrate) Tablets

RE: Response to Request for Information, AE Table Request (revised –starting and ending dates)

Dear Dr Rappaport:

Referring to a communication received from Dr. Howard Josefberg on March 27, 2006, we enclose a response to the Request for Information regarding tables for varenicline adverse events which occur in the 7 day period immediately following treatment discontinuation.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 470 KB in size.

Should you have any questions regarding this submission, please contact me at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

Michael J. Page, B.Sc. *for*
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

cc: Dr. Howard Josefberg (1 CD)
Dominic Chiapperino – Cover Letter



29 March 2006

Global Research & Development

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
c/o Central Document Room
5901-B Ammendale Road
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New Drug Application 21-928 (varenicline tartrate) Tablets

RE: Response to Request for Information, Elevated CPK Values

Dear Dr Rappaport:

Referring to a communication received from Dr. Howard Josefberg on March 20, 2006, we enclose a response to the Request for Information regarding elevated CPK values.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 4.30 MB in size.

Should you have any questions regarding this submission, please contact Mr. Michael Page at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in cursive script that reads "Michael Page".

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

cc: Dr. Howard Josefberg – 1 CD
Dominic Chiapperino – Cover Letter

3/29/06



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

DATE: March 29, 2006

TO: Robert Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Rheumatology Products

THROUGH: Claudia Karwoski, PharmD, Scientific Coordinator
Office of Drug Safety (ODS)

FROM: ODS Varenicline RMP Team

DRUG: Varenicline tartrate

NDA # 21-928

SPONSOR: Pfizer, Inc.

SUBJECT: Risk Management Plan (RMP) stamp dated November 10, 2005

PID #: D060053

EXECUTIVE SUMMARY

The Office of Drug Safety (ODS) received a consult request to review the proposed varenicline tartrate RMP which was submitted with the original NDA on November 10, 2005. The Sponsor's RMP submission includes a summary of the risk assessment conducted during the clinical development program. ODS concludes that the RMP proposal does not appear to differ from routine risk management measures, such as FDA-approved professional labeling and routine post-marketing surveillance but seems reasonable and appropriate since there were no significant safety issues identified that would warrant a Risk Minimization Action Plan (RiskMAP) or RMP.

BACKGROUND/PROPOSED RMP

Varenicline (immediate release (IR) tablet) is a partial agonist at the $\alpha 4\beta 2$ subtype neuronal nicotinic acetylcholine receptor indicated for smoking cessation. It is thought that this partial agonist of the nicotinic acetylcholine receptor is responsible for the

dependence producing effects of nicotine. This is the first drug in its chemical class and was granted propriety review.

The sponsor does not clearly identify a drug related risk in the submission, but mentions that based on the results from the non-clinical and clinical development program, areas of potential risk (effects of smoking cessation with or without treatment with varenicline) and areas with limited information (very elderly, pregnancy, adolescents, overdose) have been identified for continued routine pharmacovigilance.

The sponsor states that a principal objective of risk management and pharmacovigilance programs is the detection of adverse events that are novel or unexpected in terms of their clinical nature, severity, and/or frequency.

ODS held a meeting on March 16, 2006 with the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) to further discuss the potential need for a formalized RMP. DAARP agreed that at this time there are no safety concerns and that routine risk management measures and standard pharmacovigilance are appropriate for this product.

CONCLUSION

The Office of Drug Safety has reviewed the submitted RMP and has determined that it does not identify a specific safety concern for which a RMP to minimize risk would be normally associated. The measures proposed by the sponsor seem reasonable but would appear to be routine given the potential risk. If the sponsor or the review division identifies a safety concern and determines that a Risk Minimization Action Plan (RiskMAP) is warranted or should the review division wish ODS to review any proposed Phase IV protocols or epidemiological post-marketing studies, please send a consult to ODS and notify the ODS-IO Project Manager, Mary Dempsey, at 301-796-0147.

ODS Varenicline RMP Team

Syed Rizwanuddin Ahmad, MD, MPH, Epidemiologist, DDRE
Mary Dempsey, Project Management Officer, ODS-IO
Claudia B. Karwoski, Pharm.D., Scientific Coordinator, ODS-IO
Lauren Lee, PharmD., Safety Evaluator Team Leader, DDRE
Cheryle Milburn, Regulatory Health Project Manager, ODS-IO
Martin Pollock, PharmD, Safety Evaluator, DDRE

Claudia B. Karwoski, Pharm.D.,
Scientific Coordinator, ODS-IO

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/s/

Mary Dempsey
3/29/2006 01:14:44 PM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
3/29/2006 01:22:14 PM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-928

3/28/06

Pfizer Inc
Attention: Mike Page, Director
50 Pequot Ave
New London, CT 06320

Dear Mr. Page:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Champix (varenicline tartrate) tablets.

We also refer to the meeting between representatives of your firm and the FDA on March 1, 2006. The purpose of the meeting was to discuss the questions and discussion points raised in the IR letter dated February 24, 2006.

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

If you have any questions, call me, at (301) 796-1647.

Sincerely,

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

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/s/

Michael Folkendt
11/28/2005 04:17:32 PM
Signed for Amy Bertha.

Pfizer Inc
50 Pequot Ave
New London, CT 06320



27 March 2006

Global Research & Development

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
c/o Central Document Room
5901-B Ammendale Road
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New Drug Application 21-928 (varenicline tartrate) Tablets

RE: Response to Request for Information from Controlled Substances Staff

Dear Dr. Rappaport:

Referring to a communication received from Dr. Dominic Chiapperino on March 23, 2006, we enclose a response to the Request for Information from Dr. Katherine Bonson (CSS) for a SAS transport file including patient data from abuse liability study A3051039.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 650 KB in size.

Should you have any questions regarding this submission, please contact Mr. Michael Page at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in cursive script that reads "Michael J. Page".

Michael J. Page, B.Sc.

Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

MJP/js
Deskcopy: Dominic Chiapperino

Pfizer Inc
50 Pequot Ave
New London, CT 06320



24 March 2006

Global Research & Development

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
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New Drug Application 21-928 (varenicline tartrate) Tablets

**RE: Response to Request for Information, Varenicline common AE's by dose in <1-mg
BID dosage groups**

Dear Dr Rappaport:

Referring to a communication received from from Dr Howard Josefberg on March 21, 2006, we
enclose a response to the Request for Information. The request related to varenicline common
AE's by dose in <1-mg BID dosage groups.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0
and is virus free. This electronic submission is approximately 400 KB in size.

Should you have any questions regarding this submission, please contact Mr. Michael Page at
(860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in cursive script, appearing to read "Michael J. Page".

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

MP/js

Cc: Dr. Howard Josefberg (1CD)
Dr. Dominic Chiapperino (Cover Letter only)



Global Research & Development

23 March 2006

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation III, CDER, FDA
c/o Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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New Drug Application 21-928 (varenicline tartrate) Tablets

Re: Response to Information Request dated 20 March 2006

Dear Dr Rappaport:

With reference to an Information Request from Dr. Howard Josefberg on 20 March 2006, we attach a summary SAE cases grouped by MedDRA System Organ Class (SOC), then within SOC grouped by treatment. The categorizations requested by Dr. Josefberg are included in the table.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 455 KB in size.

Should you have any questions regarding this submission, please contact me at (860) 715-1110 or fax (860) 686-2599.

Sincerely,

A handwritten signature in black ink, appearing to read "MJP", followed by a stylized flourish.

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance



Global Research & Development

15 March 2006

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
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5901-B Ammendale Road
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New Drug Application 21-928 (varenicline tartrate) Tablets

RE: Response to Request for Information

Dear Dr Rappaport:

Referring to a communication received from from Dr Dominic Chiapperino on March 10, 2006, we enclose a response to the Request for Information. The request related to tabulation and graphical presentation of electrocardiogram data from Study A3051012.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 810 KB in size.

Should you have any questions regarding this submission, please contact me at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in cursive script, appearing to read "Mary J. Page" with a small "for" written below it.

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

cc: Dr Chiapperino – Project Manager – DAARP

Submission No. 0013



Global Research & Development

14 March 2006

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)
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New Drug Application 21-928 (varenicline tartrate) Tablets

RE: Request for Adverse Event Tables

Dear Dr Rappaport

In response to a request from Dr Howard Josefburg on 07 March 2006, we are providing "All causality" adverse event summary tables for the 'Fixed-dose, placebo-controlled Phase-2/3 studies' and the 'All completed Phase-2/3 studies' as follows:

Grouped by SOC, in decreasing order of frequency (in varenicline 1-mg BID)

All HLGTS $\geq 5\%$ in (any) varenicline group, only where \geq placebo

Each PT $\geq 1\%$ in any treatment group (within those HLGTS)

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 445 KB in size.

Should you have any questions regarding this submission, please contact Mr. Michael Page at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

Deskcopy: Dr Howard Josefburg, Medical Officer, DAARP

cc: Dr Dominic Chiapperino, Project Manager, DAARP (cover letter only)

Pfizer Inc
50 Pequot Ave
New London, CT 06320



Global Research & Development

14 March 2006

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and
Rheumatology Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
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New Drug Application 21-928 (varenicline tartrate) Tablets

General Correspondence - Response to Information Request Letter regarding Proposed Tradename

Dear Dr. Rappaport:

We refer to the above referenced pending New Drug Application and to your the Information Request Letter of 6 March 2006 relating to the acceptability of the tradename CHAMPIX.

In response to the above-referenced letter, Pfizer submits the alternate proposed tradename, "CHANTIX" for the Agency's immediate consideration for varenicline tartrate. A further back-up tradename ' [] is also proposed for consideration should CHANTIX not be acceptable. The Agency's expeditious review of these alternate names is most appreciated, as an approved name is necessary to prepare and submit revised proposed packaging and labeling well before the action date.

To assist in your review of the alternate names, we attach the results of our Dispensing Analysis report for your review (**Enclosure 1**). This report was prepared for Pfizer by []

J

While Pfizer acknowledges the Agency's objection to "CHAMPIX", this proposal remains our first choice. In this light, we are considering submitting rationale supporting "CHAMPIX" in the near future to the Agency for further consideration.

Robert Rappaport, M.D., Director
NDA 21-928

Page 2 of 2
14 March 2006

The CD-ROM has been scanned with McAfee VirusScan Enterprise version 7.1.0 and is virus free. This electronic submission is approximately 570 KB in size.

We thank you in advance for your rapid review and response. Should you have any questions regarding this submission, please contact me at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in cursive script, appearing to read "May J. Page".

Michael J. Page, B.Sc. *for*
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

MP/js
Submission No. 0010

Pfizer Inc
50 Pequot Ave
New London, CT 06320



14 March 2006

Global Research & Development

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
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New Drug Application 21-928 (varenicline tartrate) Tablets

RE: Response to Request for Information

Dear Dr Rappaport:

Referring to a Request for Information received from Dr Dominic Chiapperino on March 3, 2006, please find enclosed responses to the following questions:

Regarding the clinical efficacy and safety trials, the Sponsor should provide all data related to:

Development of physical dependence following drug discontinuation. Provide a list of all adverse events (AEs) observed in the 7-14 days following drug discontinuation in all Phase 3 studies. Include information about the method of follow-up (phone call, email, visit) with patients after drug discontinuation occurred (whether through design or study completion). For example, Study A3051035 included many patients who received OL varenicline during the 12-week run-in, and then quitters were re-randomized to receive placebo or varenicline in the double-blind treatment period of the study (another 12-weeks). Please compare Psychiatric, Nervous System, General AEs occurring in the first seven post re-randomization days, between the varenicline-to-varenicline and the varenicline-to-placebo patients.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 1.5 MB in size.

Should you have any questions regarding this submission, please contact me at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in cursive script, appearing to read "Michael J. Page".

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

cc: Dr Chiapperino – Project Manager – DAARP

Submission No. 0011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

3/13/06

NDA 21-928

INFORMATION REQUEST LETTER

Pfizer Inc
Attention: Mike Page, Director
50 Pequot Ave
New London, CT 06320

Dear Mr. Page:

Please refer to your November 9, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Champix™ (varenicline tartrate) tablets.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. These comments and requests will serve as the agenda for the March 14, 2005 teleconference between Pfizer and FDA.

1. Note that the [] described in the NDA are deemed acceptable for implementation. Additional discussion with the Agency will be needed if the results of implementation [] indicate that the pre-defined criteria for demonstrating equivalence are not achieved.
2. []
3. In our March 1, 2006 meeting, you agreed to include []

Example - []

]

[

]

4.

a.

[

]

b.

[

]

5. What is the endpoint [

]

1 Page(s) Withheld

☒ § 552(b)(4) Trade Secret / Confidential

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(4) Draft Labeling

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

Sincerely,

[See appended electronic signature page]

Chi-wan Chen, Ph.D.
Deputy Director
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Chi Wan Chen
3/13/2006 02:34:44 PM



10 March 2006

Global Research & Development

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)
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OF PFIZER INC.

New Drug Application 21-928 (varenicline tartrate) Tablets

RE: Response to Request for Information

Dear Dr Rappaport:

Referring to a Requests for Information received from from Dr Dominic Chiapperino on
March 3rd 2006, please find enclosed responses to the following questions:

Regarding Study A3051039 (human abuse liability study in drug abusers), the Sponsor should provide the following:

- 1) Complete drug histories for each subject enrolled in the abuse liability study.*
- 2) Tables for each separate subjective measure, constructed with drug treatments (and placebo) as column headings and individual subject responses (represented as peak values within first 6 hr) in each row. Separate tables should be constructed for smokers and non-smokers. Means and standard errors should be at the bottom of each treatment column. Statistically significant differences from placebo should be noted, with p values.*
- 3) Similar tables should be constructed for responses reported in the Amphetamine Qualifying Procedure (AQP) for each of the 4 subjective measures, with subjects grouped by smoking status.*

Regarding the clinical efficacy and safety trials, the Sponsor should provide all data related to:

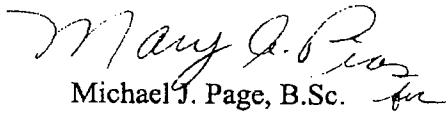
- 1) Development of tolerance to either the therapeutic effects or adverse events (e.g., increasing drug ingestion to maintain therapeutic effect, reduction in adverse events with continued drug administration).*

A further submission, responding to the remaining query contained in the March 3rd request will be provided on Tuesday March 14, 2006.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 1 MB in size.

Should you have any questions regarding this submission, please contact me at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,



Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

cc: Dr. Dominic Chiapperino – Regulatory Project Manager, DAARP

Worldwide Development
Pfizer Inc
50 Pequot Ave
New London, CT 06320



08 March 2006

Global Research & Development

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
c/o Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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OF PFIZER INC.

New Drug Application 21-928 (varenicline tartrate) Tablets

RE: Request for Updated CTD Files

Dear Dr Rappaport:

In response to a request from Dr. Howard Josefburg on 06 March 2006, we are providing an updated version of CTD Sections 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety) for the above referenced New Drug Application. These versions have been updated for more conveniently bookmarked table titles to facilitate efficient navigation. No data has been altered from the versions filed in the initial NDA.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 22 MB in size.

Should you have any questions regarding this submission, please contact Mr. Michael Page at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in cursive script, appearing to read "Michael J. Page".

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

MEMO

To: Robert Rappaport, M.D.
Director, Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-130

From: Jinhee L. Jahng, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420; White Oak Bldg. 22, Mail Stop 4447

Through: Alina R. Mahmud, R.Ph., M.S., Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420; White Oak Bldg. 22, Mail Stop 4447

Date: March 6, 2006

Re: ODS Consult 06-0053
Champix (Varenicline tartrate tablets) 0.5 mg and 1 mg
NDA#: 21-928

This memorandum is in response to a January 26, 2006 request from your Division for a review of the proprietary name, Champix (NDA#: 21-928). Upon the initial steps in the proprietary name review process (EPD), the Division of Drug Marketing, Advertising and Communications (DDMAC) did not recommend the use of the proposed proprietary name Champix from a promotional perspective because it is overly fanciful and overstates the efficacy of the product. DDMAC provided the following comments:

“DDMAC objects to the proposed trade name "Champix" because [

]

Given our limited information, [

The Federal Food, Drug, and Cosmetic Act provides 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. [*See* 21 U.S.C. §§ 352(a) & (n). *See also* 21 C.F.R. §§ 202.1(e)(5)(i), (e)(6)(i).]

As per email correspondence with the Division of Anesthesia, Analgesia, and Rheumatology Products Project Manager, Dominic Chiapperino, on March 3, 2006, the Division concurs with DDMAC's comments. Therefore, DMETS will not proceed with the safety review of the proposed proprietary name, Champix, since the Division supports DDMAC's objection of the name based on promotional concerns.

If you have any questions for DDMAC, please contact Catherine Gray or Suzanne Berkman at 301-796-1200. If you have any other questions or need clarification, please contact the medication errors project manager, Diane Smith, at 301-796-0538.

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On Original**

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/s/

Jinhee Jahng
3/6/2006 04:39:04 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
3/7/2006 09:36:22 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/7/2006 10:35:41 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/7/2006 12:53:42 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>		
TO (Division/Office): Mail: Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22, RM 4447		FROM: Dominic Chiapperino, Ph.D. Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170) 301-796-1183 chiapperinod@cder.fda.gov Building 22, Rm. 3115		
DATE 3/21/06	IND NO.	NDA NO. 21-928	TYPE OF DOCUMENT New submission	DATE OF DOCUMENT November 10, 2006
NAME OF DRUG Varenicline tartrate		PRIORITY CONSIDERATION Yes, granted priority review	CLASSIFICATION OF DRUG 1 P	DESIRED COMPLETION DATE April 1, 2006
NAME OF FIRM: Pfizer				
REASON FOR REQUEST I. GENERAL				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"><input type="checkbox"/> NEW PROTOCOL</div> <div style="width: 33%;"><input type="checkbox"/> PRE-NDA MEETING</div> <div style="width: 33%;"><input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER</div> <div style="width: 33%;"><input type="checkbox"/> PROGRESS REPORT</div> <div style="width: 33%;"><input type="checkbox"/> END OF PHASE II MEETING</div> <div style="width: 33%;"><input type="checkbox"/> FINAL PRINTED LABELING</div> <div style="width: 33%;"><input type="checkbox"/> NEW CORRESPONDENCE</div> <div style="width: 33%;"><input type="checkbox"/> RESUBMISSION</div> <div style="width: 33%;"><input type="checkbox"/> LABELING REVISION</div> <div style="width: 33%;"><input type="checkbox"/> DRUG ADVERTISING</div> <div style="width: 33%;"><input type="checkbox"/> SAFETY/EFFICACY</div> <div style="width: 33%;"><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE</div> <div style="width: 33%;"><input type="checkbox"/> ADVERSE REACTION REPORT</div> <div style="width: 33%;"><input type="checkbox"/> PAPER NDA</div> <div style="width: 33%;"><input type="checkbox"/> FORMULATIVE REVIEW</div> <div style="width: 33%;"><input type="checkbox"/> MANUFACTURING CHANGE/ADDITION</div> <div style="width: 33%;"><input type="checkbox"/> CONTROL SUPPLEMENT</div> <div style="width: 33%;"><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Tradename review</div> <div style="width: 33%;"><input type="checkbox"/> MEETING PLANNED BY</div> </div>				
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 checked="" 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: Please review proposed new tradenames [] and Chantix for safety issues as soon as possible. These were submitted by Pfizer on March 14, 2006, currently in the EDR. The action package is due to Kurt Rosebraugh for April 18, 2006 and Bob Rappaport April 4, 2006.				
SIGNATURE OF REQUESTER Dominic Chiapperino (electronic)		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Dominic Chiapperino
3/22/2006 04:43:42 PM

Worldwide Development
Pfizer Inc
50 Pequot Ave
New London, CT 06320



Global Research & Development

3 March 2006

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
10903 New Hampshire Avenue
Building 22 Room 3168
Silver Spring, MD 20993-0002

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New Drug Application 21-928 CHAMPIX™ (varenicline tartrate) Tablets

RE: General Correspondence – Request for DAARP discussion with Office of Compliance to allow pre-approval importation of Champix tablets by March 9, 2006 in order to assure timely launch of product

Dear Dr Rappaport:

The above referenced New Drug Application is currently being assessed by the Division of Anesthesia, Analgesia and Rheumatology Products with a PDUFA priority review action date of 10 May 2006. If the application is approved at or near that time, Pfizer intends to make the product available to patients as quickly as possible, most likely by the end of July 2006.

In order to build on the priority review determination by the Division, we believe it is incumbent upon Pfizer that Champix tablets be made available as soon as possible after approval. In this way, we optimize the opportunity for the patient population to benefit from the advantages of the accelerated evaluation.

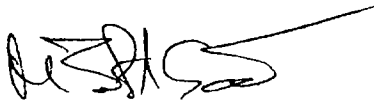
Champix tablets are manufactured in the Pfizer manufacturing plant in Illertissen, Germany and will be packaged for US distribution at []

To attain the July launch date, we must initiate packaging of the product in March 2006, and must import the drug product no later than March 10, 2006. Since this import would be of a currently unapproved new drug, we would be grateful if you would confirm with the Office of Compliance that this importation is acceptable in order to avoid detention of the product at US Customs in Chicago.

Pfizer notes that this communication makes no assumptions on, and is without prejudice to, any FDA decision on the ongoing NDA review. Furthermore, should an approval not be forthcoming, Pfizer commits to re-export any imported drug product.

Should you have any questions regarding this submission, please contact me at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in black ink, appearing to read 'Michael J. Page', with a long horizontal stroke extending to the right.

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc



Global Research & Development

3 March 2006

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
c/o Central Document Room
5901-B Ammendale Road
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OF PFIZER INC.

New Drug Application 21-928 CHAMPIX™ (varenicline tartrate) Tablets

RE: Response to Request for Information

Dear Dr Rappaport:

With regard to communication from Dr Dominic Chiapperino on February 28, 2006, please find enclosed responses to the respective Requests for Information.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 78 MB in size.

Should you have any questions regarding this submission, please contact me on (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in black ink, appearing to read "MJ Page", with a long horizontal flourish extending to the right.

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

MP/js
Enclosure (1 CD)

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 1, 2006
TIME: 2:30 pm- 4:00 pm
APPLICATION: NDA 21-928
DRUG NAME: Champix (varenicline tartrate) tablets
TYPE OF MEETING: Type C
MEETING CHAIR: Moheb Nasr
MEETING RECORDER: Amy Bertha

MAR 27 2006

FDA ATTENDEES:

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Moheb Nasr, Director
Chi-wan Chen, Deputy Directory
Rik Lostritto, Director, Division of Pre-Marketing Assessment III
Ravi Harapanhalli, Branch Chief, Division of Pre-Marketing Assessment III
Ying Wang, Review Chemist, Manufacturing Sciences Branch
Steve Miller, Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment II
Amy Bertha, Regulatory Health Project Manager

OFFICE OF NEW DRUGS

Division of Anesthesia, Analgesia, Rheumatology
Dan Mellon, Team Leader, Pharmacology/Toxicology
Dominic Chiapperino, Regulatory Health Project Manager

OFFICE OF COMPLIANCE

Albinus D'Sa, Compliance Officer

OFFICE OF REGULATORY AFFAIRS

Robert Coleman, Investigator

EXTERNAL CONSTITUENT ATTENDEES:

Jeff Blumenstein, Global Head, Global Regulatory CMC/QA
Roger Nosal, Executive Director, Global Regulatory CMC
Tom Garcia, Associate Director, Global Regulatory CMC
Tom Hutchinson, Senior Director, Global Manufacturing Compliance (New Products)
Frank Busch, Research Fellow, Development API
Mary am Ende, Associate Research Fellow, Solids & PE Development
Tim Graul, Senior Principal Scientist, Development Analytical
Mike Page, Director, Regulatory Strategy and Registration
Vince McCurdy, Research Fellow,
Kim Vukovsky, Director, Non-Clinical Statistics

BACKGROUND:

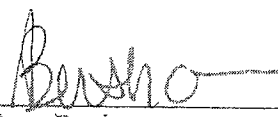
Varenicline tartrate [] NDA 21-928
was submitted to the FDA on November 10, 2006. The purpose of this meeting was to discuss the questions and discussion points outlined in the IR letter dated February 24, 2006.

THE MEETING:

Pfizer presented portions of the attached slides in the meeting (Slides 1-14, 27-37, 54-56, and 59-64). The slides facilitated the discussion and addressed several questions outlined in the IR letter. The attached slide presentation serves as the preliminary responses to the IR letter questions. Pfizer is planning on sending their official answer to the IR letter in the form of an NDA amendment.

During the meeting discussion, FDA and Pfizer agreed that for potential genotoxic impurities that are predicted to act via either a direct or common mechanism, the safety evaluation should be based on the sum of the individual impurities rather than on levels of each impurity

Minutes Preparer: _____


Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment

Chair Concurrence: _____


Moheb Nasr
Director
Office of New Drug Quality Assessment

50 Page(s) Withheld

☒ § 552(b)(4) Trade Secret / Confidential

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(4) Draft Labeling

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/s/

Amy Bertha

3/28/2006 09:18:22 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

2-24-06

NDA 21-928

INFORMATION REQUEST LETTER

Pfizer Inc
Attention: Mike Page, Director
50 Pequot Ave
New London, CT 06320

Dear Mr. Page:

Please refer to your November 9, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Champix™ (varenicline tartrate) tablets.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. These comments/requests and additional discussion points will serve as the agenda for the March 1, 2005 meeting between Pfizer and FDA.

Information Requests:

1. [

b.

c.

2. [

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

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

Sincerely,

{See appended electronic signature page}

Chi-wan Chen, Ph.D.
Deputy Director
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

1 Page(s) Withheld

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 § 552(b)(4) Draft Labeling

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/s/

Chi Wan Chen

2/24/2006 01:11:19 PM



13 February 2006

Global Research & Development

Robert Rappaport, M.D., Director
Division of Anesthetic, Analgesic and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
c/o Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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NDA 21-928: CHAMPIX (varenicline tartrate) Tablets

Response to FDA Request for Information

Dear Dr Rappaport:

We refer to e-mail correspondence from Dr. Dominic Chiapperino, Project Manager received on 27-January-2006 requesting information to aid the Controlled Substances Staff in their review of the abuse liability information provided in NDA-21,928 for CHAMPIX and to our submission on 3-February 2003.

With this submission, we are providing a response as outlined in the attached document.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free.

Should you have any questions regarding this submission, please contact Mr. Michael Page at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

Michael J. Page

Michael J. Page, B.Sc.

Director

Worldwide Regulatory Strategy

Worldwide Regulatory Affairs and Quality Assurance

Pfizer Inc

Enclosure

cc: Katherine Bonson, Ph.D., Controlled Substances Staff (cover letter)
Dominic Chiapperino, Ph.D., Regulatory Project Manager (cover letter)

Pfizer Inc
50 Pequot Ave
New London, CT 06320



Global Research & Development

9 February 2006

Robert Rappaport, M.D., Director
Division of Anesthetic, Analgesic and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
c/o Central Document Room
5901-B Ammendale Road
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
**RE: New Drug Application 21-928 CHAMPIX™ (varenicline tartrate) Tablets
Three-Month Safety Update**

Dear Dr Rappaport:

We refer to the pending New Drug Application (NDA 21-928) for CHAMPIX™
(varenicline tartrate), submitted on 10-November-2005 and filed in accordance with 21 CFR
314.101(a) on January 23, 2006.

We also refer to the 21-November-2005 submission (IND 58,994 Serial #0159) of our proposal
for the safety update for this application.

In accordance with 21 CFR §314.50(d)(5)(vi)(b), Pfizer hereby submits a Safety
Update report for NDA 21-928.

Also provided in this submission is the final clinical study report .

J

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0
and is virus free. This electronic submission is approximately 15 MB in size.

Should you have any questions regarding this submission, please contact Mr. Michael Page at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in cursive script, appearing to read "Michael J. Page".

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

MJP/js

Enclosure (CD Rom)

cc: Dominic Chiapperino, Ph.D., Regulatory Project Manager (cover letter)

Submission No. 0004



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-928

2-8-06

Pfizer Inc
Attention: Mike Page, Director
50 Pequot Ave
New London, CT 06320

Dear Mr. Page:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Champix (varenicline tartarate) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on January 5, 2006. The purpose of the meeting was to discuss CMC issues, L

J

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

If you have any questions, call me, at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE MINUTES

TELECONFERENCE DATE: January 5, 2006

TIME: 3:00 pm- 3:30 pm FEB - 7 2006

APPLICATION: NDA 21-928

DRUG NAME: Champix (varenicline tartrate) tablets

TYPE OF TELECONFERENCE: Type C

TELECONFERENCE CHAIR: Moheb Nasr

TELECONFERENCE RECORDER: Amy Bertha

FDA ATTENDEES:

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Moheb Nasr, Director

Chi-wan Chen, Deputy Directory

Ravi Harapanhalli, Branch Chief, Division of Pre-Marketing Assessment III

Ying Wang, Chemist, Manufacturing Sciences Branch

Steve Miller, Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment II

Amy Bertha, Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Robert Baum., Executive Director, Global Regulatory CMC Policy

Roger Nosal, Senior Director, Global Regulatory CMC

Tom Garcia, Associate Director, Global Regulatory CMC

BACKGROUND:

Varenicline tartrate (NDA 21-928) [

The purpose of this teleconference was to discuss FDA's early CMC observations of the NDA review.]

THE MEETING:

- Pfizer agreed to send a word version of both the [] to Amy Bertha. FDA is planning []

- []

]

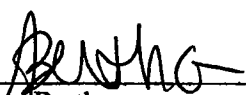
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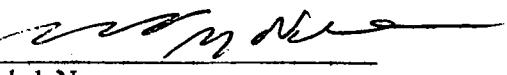
- [

- [

- Pfizer proposed to [

] FDA asked if Pfizer would amend [portions of the NDA, and Pfizer agreed. FDA reminded Pfizer that the amendment should be submitted as soon as possible, in order to not cause a delay in the review.]

Minutes Preparer: 
Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment

Chair Concurrence: 
Moheb Nasr
Director
Office of New Drug Quality Assessment

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/s/

Amy Bertha
2/8/2006 10:32:10 AM

Pfizer Inc
50 Pequot Ave
New London, CT 06320



Global Research & Development

7 February 2006

Robert Rappaport, M.D., Director
Division of Anesthetic, Analgesic and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
c/o Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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OF PFIZER INC.

New Drug Application 21-928 CHAMPIX™ (varenicline tartrate) Tablets

RE: Minor Amendment – Stability Update

Dear Dr Rappaport:

We refer to the Type C meeting held on 14-October-2004. At this meeting Pfizer requested and received FDA agreement to submit additional stability data during the review of the varenicline tartrate NDA. This request was confirmed during a 6-January-2006 teleconference with Moheb Nasr, Ph.D., Director of the Office of New Drug Quality Assessment and ONDQA staff.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 12.5 MB in size.

Should you have any questions regarding this submission, please contact me at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in black ink, appearing to read "MJP", with a long horizontal line extending to the right.

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc



Global Research & Development

3 February 2006

Robert Rappaport, M.D., Director
Division of Anesthetic, Analgesic and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
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New Drug Application 21-928 CHAMPIX™ (varenicline tartrate) Tablets

RE: Response to Query

Dear Dr Rappaport:

We refer to the email correspondence from Dr Dominic Chiapperino, received on 27 January 2006. This detailed 5 questions as follows:

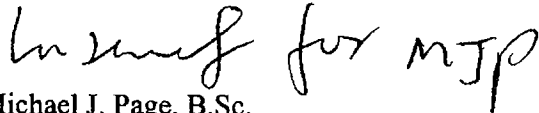
1. *In the "Assessment of Abuse Potential of Varenicline" section of the NDA, the Sponsor should provide active links for each study mentioned in the summary to: the original protocol, the individual and summed data, and any statistical analysis conducted on the data.*
2. *For Protocol A3051039 (the varenicline human abuse liability study in drug abusers), the Sponsor should provide the following information about the Amphetamine Qualifying Procedure: the individual and summed data, the time frames when subjective and objective measures were obtained, the timecourse of the subjective and objective responses, and any statistical analysis conducted on the data.*
3. *Provide a link or other directions for the SAS files for the human abuse liability study.*
4. *Provide receptor binding data in Ki's, as opposed to IC50 values.*
5. *Please locate receptor binding data studies with selective opioid radioligands, if they exist.*

This submission provides Pfizer responses to Questions 1, 4 and 5. As discussed on the telephone with Dr Chiapperino, the data requested in Question 2 is being gathered from the investigator site and will be forwarded once available. We will provide a response to Q3 following clarification on the issue from Dr Chiapperino.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 10 MB in size.

Should you have any questions regarding this submission, please contact Mr. Michael Page at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

A handwritten signature in black ink that reads "In brief for MJP". The signature is written in a cursive, flowing style.

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

MP/js

Submission No. 0003



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-928

1/31/06

Pfizer Inc
Attention: Michael Page, Director
50 Pequot Ave
New London, CT 06320

Dear Mr. Page:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Champix™ (varenicline tartrate) tablets.

We also refer to your January 13, 2006, correspondence, received January 17, 2006, requesting a two part meeting:

J

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C 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: March 1, 2006

Time: 2:00 pm – 4:00 pm

Location: Food and Drug Administration
White Oak CDER Building #22 Room 1315
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Invited CDER participants:

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Moheb Nasr, Director

Chi-Wan Chen, Deputy Director

Rik Lostritto, Director, Division of New Drug Quality Assessment I (Part 1 only)

Elaine Morefield, Director, Division of New Drug Quality Assessment II (Part 1 only)

John Simmons, Director, Division of New Drug Quality Assessment III

Eric Duffy, Director, Division of Post-Marketing Evaluation (Part 1 only)

Ravi Haraphanalli, Branch Chief, Division of New Drug Quality Assessment III

Stephen Miller, Pharm. Assessment Lead, Division of New Drug Quality Assessment II

Ying Wang, Chemistry Reviewer, Manufacturing Sciences Branch
Michael Folkendt, Supervisory Project Manager
Amy Bertha, Regulatory Health Project Manager

OFFICE OF COMPLIANCE

Division of Manufacturing and Product Quality

Nicholas Buhay, Director
Albinus D Sa, Consumer Safety Officer

OFFICE OF REGULATORY AFFAIRS

Robert Coleman, Field Investigator (Part 2 only)

OFFICE OF NEW DRUGS

Division of Anesthesia, Analgesia, and Rheumatology Products

Robert Rappaport, Director (Part 2 only)
Howard Josefberg, Medical Officer (Part 2 only)
Dominic Chiapperino, Regulatory Health Project Manager (Part 2 only)

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 me at amy.bertha@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 the following number to request an escort to the conference room: Amy Bertha, (301) 796-1647.

Provide the background information for this meeting (three copies to the NDA and 20 desk copies to me) by February 21, 2006.

If you have any questions, call me, at (301) 796-1647.

Sincerely,

(See appended electronic signature page)

Amy Bertha
Regulatory Health Project Manager
Division of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Amy Bertha
1/31/2006 06:02:52 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-928

Pfizer, Inc
50 Pequot Avenue
New London, CT 06320

1-23-06

Attention: Michael J. Page, B.Sc.
Director, Worldwide Regulatory Strategy

Dear Mr. Page:

Please refer to your November 9, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Champix (varenicline tartrate; CP-526,555) Tablets, 0.5 and 1.0 mg.

We also refer to your submission dated January 13, 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 January 23, 2006, in accordance with 21 CFR 314.101(a).

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 Dominic Chiapperino, Ph.D., Regulatory Project Manager, at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia,
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
1/23/2006 05:17:32 PM

Pfizer Inc
50 Pequot Ave
New London, CT 06320



13 January 2006

Global Research & Development

Robert Rappaport, M.D., Director
Division of Anesthetic, Analgesic and Rheumatology
Products (HFD-170)
Office of Drug Evaluation III, CDER, FDA
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OF PFIZER INC.

NDA 21-928: CHAMPIX™ (varenicline tartrate) Tablets

RE: Request for Type C Meeting – Chemistry, Manufacturing and Controls

Dear Dr. Rappaport:

With the submission, we are formally requesting a Type C meeting to discuss Chemistry, Manufacturing and Controls information provided in our 09-November-2005 NDA submission.

We refer to a teleconference held on 05 January 2006 between staff from the Office of New Drug Quality Assessment (ONDQA) and Pfizer Regulatory CMC. During the teleconference FDA suggested a meeting with Pfizer on 01 March 2006 to discuss comments and issues revealed by the reviewing chemists up to that point. In order to progress this meeting, it was suggested that Pfizer apply formally for a Type C consultation. ONDQA also requested Pfizer to present.

The attached document provides the information pertinent to a formal Type C meeting request.

The CD Rom has been scanned for viruses using McAfee VirusScan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 415 KB in size.

Should you have any questions regarding this submission, please contact me at (860) 715 1110 (phone) or (860) 686 2599 (fax).

Sincerely,

Michael J. Page, B.Sc.
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc

cc: Ms. Amy Bertha – Project Manager – Office of New Drug Quality Assessment
Submission No. 0001

Product Name and Application Number	Varenicline Tartrate (CP-526,555-18) NDA 21-928
Chemical Name	<p>CAS Name: 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate</p> <p>Molecular Weight: 361.36 Molecular Formula: C₁₃H₁₃N₃ • C₄H₆O₆ (L-tartrate salt)</p>
Proposed Indication	Smoking cessation
Type of Meeting Requested	Type C
Previous Agency Interaction	[
Introduction	<p>Varenicline tartrate is a nicotinic receptor partial agonist in development for smoking cessation. This compound has high affinity for the $\alpha 4 \beta 2$ neuronal nicotinic receptor subtype that mediates the reinforcing effects of nicotine. The results of preclinical pharmacology and toxicology studies to date have established that varenicline tartrate is a selective, potent, centrally active $\alpha 4 \beta 2$ partial agonist, which appears to be neither, mutagenic, clastogenic, teratogenic and is not associated with any unexpected adverse effects.</p> <p>The intended commercial dosage form for varenicline tartrate is a conventional, film-coated tablet, containing 0.5 mg and 1.0 mg of drug substance.</p>
Purpose of Meeting	<p>The following topics are presented for discussion:</p> <p>• [</p>

Varenicline Tartrate NDA 21-928: CMC Meeting Request

	<ul style="list-style-type: none"> Obtain comments and feedback from FDA reviewing chemists (up to this point) regarding their review of the varenicline Present a general overview of Pfizer to FDA staff.
Specific Objectives/ Outcomes expected from the Meeting	<ol style="list-style-type: none"> Present a general overview of Pfizer FDA staff. Clarification of questions/issues raised by FDA during their review of the varenicline Ongoing dialogue related to Pfizer
Preliminary Proposed Agenda	<p>Suggested Length of Meeting - 2 hours</p> <p>General overview of Pfizer 60 minutes</p> <p>Discussion of feedback/comments from reviewing chemists regarding their review of the varenicline 60 minutes</p>
List of Individuals who will attend the Proposed Meeting from Pfizer	<p>Thomas Garcia - Regulatory CMC, Associate Director</p> <p>Roger Nosal - Regulatory CMC, Executive Director</p> <p>Vincent McCurdy - Science and Technology,</p> <p>Jeff Blumenstein - Global Regulatory CMC/QA, Vice President</p> <p>Mike Page - Director, Worldwide Regulatory Affairs</p> <p>Mary am Ende - Solids and PE Development, Associate Research Fellow</p> <p>Timothy Graul - Principal Scientist, Analytical R&D</p> <p>Frank Busch - Research Fellow, Chemical R&D</p> <p>Representative from Pfizer Global Manufacturing (to be named)</p>

Varenicline Tartrate NDA 21-928: CMC Meeting Request

List of Agency Staff requested by the Sponsor to participate in the Proposed Meeting	<p>OFFICE OF NEW DRUG QUALITY ASSESSMENT</p> <p>Moheb Nasr, Director Chi-Wan Chen, Deputy Director Guirag Poochikian, Associate Director for Regulatory Science Michael Folkendt, Supervisory Project Manager John Simmons, Director, Division of Pre-Marketing Assessment III Ravi Harapanhalli, Branch Chief, Division of Pre-Marketing Assessment III Ying Wang, Chemist, Division of Manufacturing Sciences Steve Miller, Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment II Amy Bertha, Regulatory Health Project Manager</p> <p>OFFICE OF COMPLIANCE, DIVISION OF MANUFACTURING AND PRODUCT QUALITY</p> <p>John Dietrick, Team Leader Kris Evans, Sr. Reg. Operations Zi Qiang Gu, Consumer Safety Officer</p> <p>OFFICE OF REGULATORY AFFAIRS, DIVISION OF FIELD INVESTIGATIONS</p> <p>Bob Coleman, Consumer Safety Officer</p> <p>OFFICE OF NEW DRUGS</p> <p>Rigo Roca, Deputy Director</p>
Approximate Date when supporting Documentation will be sent to the Division	15-February-2006
Suggested Meeting Dates	1-March-2006; 2:00 – 4:00

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>				
TO (Office/Division): Yi Tsong, Ph.D. - OPSS/OB/QMRS			FROM (Name, Office/Division, and Phone Number of Requestor): Corinne P. Moody, Science Policy Analyst - HFD-009, Controlled Substance Staff				
DATE January 11, 2006	IND NO.	NDA NO. 21-928	TYPE OF DOCUMENT	DATE OF DOCUMENT November 10, 2005			
NAME OF DRUG Varenicline tartrate	PRIORITY CONSIDERATION High		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 01-25-06			
NAME OF FIRM:							
REASON FOR REQUEST							
I. GENERAL							
<table style="width: 100%; border: none;"> <tr> <td style="vertical-align: top; width: 33%;"> <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 </td> <td style="vertical-align: top; width: 33%;"> <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 </td> <td style="vertical-align: top; width: 33%;"> <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 type="checkbox"/> OTHER (SPECIFY BELOW): </td> </tr> </table>					<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 type="checkbox"/> OTHER (SPECIFY BELOW):
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II. BIOMETRICS							
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III. BIOPHARMACEUTICS							
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IV. DRUG SAFETY							
<table style="width: 100%; border: none;"> <tr> <td style="vertical-align: top; width: 50%;"> <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 </td> <td style="vertical-align: top; width: 50%;"> <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS </td> </tr> </table>					<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	
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V. SCIENTIFIC INVESTIGATIONS							
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<input type="checkbox"/> CLINICAL	<input type="checkbox"/> NONCLINICAL						
COMMENTS / SPECIAL INSTRUCTIONS: Please conduct a statistical analysis of the human abuse liability study for varenicline. The NDA is located in the EDR. If you have any questions, please feel free to contact me at (301) 827-1999.							
SIGNATURE OF REQUESTOR Corinne P. Moody, Science Policy Analyst			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND				
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER				

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/s/

Corinne Moody
1/11/2006 04:58:07 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 58,994

12-29-05

Pfizer Inc.
50 Pequot Avenue
New London, CT 06320

Attention: Mike Page
Director, Worldwide Regulatory Affairs
Pfizer Global Research & Development

Dear Mr. Page:

Please refer to your Investigational New Drug Application (IND) for Varenicline Tartrate.

We also refer to the meeting between representatives of Pfizer and the FDA on August 18th, 2005. The purpose of the meeting was to discuss the determination of abuse liability and the analysis of data from Protocol 3019.

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

If you have any questions, call me at (301) 827-1620.

Sincerely,

(Signature of Dominic Chiapperino)

Dominic Chiapperino, Ph.D.
Regulatory Project Manager
Office of Anesthesia, Analgesia, and
Perianesthesia Practice
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Best Possible Copy

MEMORANDUM OF TELECONFERENCE MINUTES

TELECONFERENCE DATE: January 5, 2006
TIME: 3:00 pm- 3:30 pm FEB - 7 2006
APPLICATION: NDA 21-928
DRUG NAME: Champix (varenicline tartrate) tablets
TYPE OF TELECONFERENCE: Type C
TELECONFERENCE CHAIR: Moheb Nasr
TELECONFERENCE RECORDER: Amy Bertha

FDA ATTENDEES:

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Moheb Nasr, Director
Chi-wan Chen, Deputy Directory
Ravi Harapanhalli, Branch Chief, Division of Pre-Marketing Assessment III
Ying Wang, Chemist, Manufacturing Sciences Branch
Steve Miller, Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment II
Amy Bertha, Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Robert Baum., Executive Director, Global Regulatory CMC Policy
Roger Nosal, Senior Director, Global Regulatory CMC
Tom Garcia, Associate Director, Global Regulatory CMC

BACKGROUND:

Varenicline tartrate (NDA 21-928) ☐

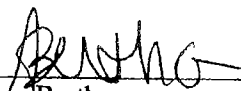
The purpose of this teleconference was to discuss FDA's early CMC observations of the NDA review. J

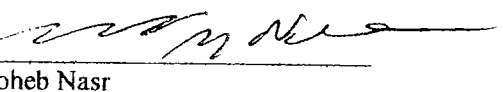
THE MEETING:

- Pfizer agreed to send a word version of both the ☐ J to Amy Bertha. FDA is planning ☐

- ☐

- [
- [
- [
- Pfizer proposed [
-] FDA asked if Pfizer would amend [
-]

Minutes Preparer: 
Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment

Chair Concurrence: 
Moheb Nasr
Director
Office of New Drug Quality Assessment

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/s/

Amy Bertha
2/8/2006 10:32:10 AM

Industry Meeting Minutes

Date/Time: June 9, 2005/2:30 - 4:00 pm
Location: Parklawn Building, Potomac Conference Room
Application: IND 58,994
Sponsor: Pfizer Inc.
Drug/Dosage Form/Doses: Varenicline Tartrate Controlled Release
Indication: Smoking Cessation
Type of Meeting: Type B (Pre-NDA)
Meeting Chair: Celia Winchell, M.D., Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Minutes Recorder: Dominic Chiapperino, Ph.D., Regulatory Project Manager, DAARP

Pfizer	Title
Mr. Mike Page	Director, Worldwide Regulatory Affairs
Dr. Saloman Azoulay	Vice President, Full Development Team Leader
Dr. Karen Reeves	Executive Director, Global Clinical Leader
Dr. Bill Billings	Associate Director, Clinical Biostatistics
Dr. Aaron Burstein	Associate Director, Clinical Sciences
Dr. Helene Faessel	Associate Director, Clinical PK/PD
Dr. Steve Sands	Associate Research Fellow, Neurosciences Biology
Dr. Martin Finkelstein	Associate Research Fellow, Toxicology Sciences
Mrs. Mary Pias	Senior Associate, Worldwide Regulatory Strategy
Mrs. Jacqueline Simonds	Associate, Electronic Submissions, Worldwide Regulatory Operations
Dr. Christine Baker	Manager, Worldwide Outcomes Research
Dr. Phyllis Christesen	Director, US Regulatory Affairs
Dr. Mark Ammann	Senior Director, Worldwide Regulatory Affairs
FDA	Title
Rigoberto Roca, M.D.	Deputy Division Director
Thomas J. Permutt, Ph.D.	Team Leader, Statistics
Howard Josefberg, M.D.	Medical Officer, Addiction Products
Mamata De, Ph.D.	Pharmacology/Toxicology Reviewer
Srikanth Nallani, Ph.D.	Biopharmaceutics Reviewer
Joan Buenconsejo, Ph.D.	Statistics Reviewer
Jane Scott, Ph.D.	Reviewer, Study Endpoints and Label Development Team
Dominic Chiapperino, Ph.D.	Regulatory Project Manager

Meeting Objective(s): The discussion of Pfizer's proposed clinical development program for Varenicline Tartrate Controlled Release and planned eCTD NDA submission.

General Discussion: Following introductions, the discussion focused on Pfizer's questions that were included in the June 9, 2005, meeting package and June 9, 2005, amendment to the meeting package. The questions are presented below in *italicized* text in the order in which they were

addressed at the meeting. Agency responses, prepared prior to the meeting and presented on slides, are **bolded**. Discussion is presented in normal text.

Pharmacology/Toxicology Comments

- **Impurity/degradation product safety qualification data should be submitted with the NDA.**
- **As previously noted, the carcinogenicity study reports should be submitted with the NDA.**
- **A π study should be completed to support your proposed pediatric study.**
- **The NDA submission should evaluate the reproduction and developmental toxicity findings for varenicline in light of the extensive literature describing nicotine/tobacco related reproductive and developmental toxicity.**

Discussion:

The Sponsor questioned whether a π study would be needed if the product would only be for use in adolescents in the pediatric population. The Agency responded that the π study would not be required under those circumstances. The Division expressed concern regarding some findings reported in the Segment III reproduction study, specifically changes in behavioral patterns noted in the F1 generation, and recommended that the Sponsor specifically discuss these findings and provide their rationale whether or not they believe these data should be explored further.

Question 1: Efficacy Program and Presentation of Efficacy Data: Does the Division concur that appropriate and adequate efficacy studies have been conducted to support the review of an NDA?

FDA Response

- **Yes**

Question 2: Efficacy Program and Presentation of Efficacy Data: Does the Division concur that the proposed presentation of data is appropriate to support review of an NDA?

FDA RESPONSE

- **Yes, for the most part**
- **Note that pooled analyses are considered exploratory. To support the envisioned comparative claim, data from two independent trials, each providing evidence of superiority, would be needed.**
- **All requirements detailed in the US Code of Federal Regulations must be satisfied, either in addition to, or in lieu of CTD specifications**

Discussion:

The Sponsor stated that, in all Phase 3 studies, the database was now locked down and superiority over Zyban had been demonstrated.

Question 3: Safety Program and Presentation of Safety Data: Does the Division concur that appropriate and adequate safety evaluations have been conducted to support the review of an NDA?

FDA RESPONSE

- Overall extent and duration of exposure will be adequate
- A prospectively designed QTc prolongation study will not be required for filing the NDA
- Should a cardiac conduction safety signal be identified, however, such a study would be required
 - Described in ICH draft guidance E14
- Potential for CYP induction by varenicline should be evaluated
 - Initially, adequately conducted *in vitro* studies are acceptable
 - Additional studies may be required based on *in vitro* study results
- In renal impairment patients: Justify why the dosage adjustment recommended is 1 mg QD, rather than 0.5 mg (or lower dose) b.i.d., given that the recommended dose for patients with normal renal function is 1 mg b.i.d.

Discussion:

The Agency requested that the Sponsor submit all safety data obtained in Phase 1, 2, and 3 studies in a manner that allows integrated review.

Question 4: Does the division concur with the safety data presentation?

FDA RESPONSE:

- Presentation and inclusion of the safety data should be consistent with the 7/1988 Agency guidance *Format and Content of the Clinical and Statistical Sections of an Application*.
- Integrated exposure and AE data should be presented
 - Across all Phase 1 studies
 - Across all clinical study groupings as described

Your proposed presentation of safety data states:

‘AEs will be summarized by System Organ Class (SOC) and also tabulated with incidence and severity. Within SOC, preferred terms will be ordered alphabetically.’

- AE presentations and tabulations should group by System Organ Class, High Level Group Term, and Preferred Term

- **Datasets should include System Organ Class, High Level Group Term, Preferred Term and Verbatim Term**
- **A thesaurus showing which verbatim terms are subsumed under each preferred term is helpful.**

Discussion:

The Agency indicated that it was not made clear how safety data from abuse liability studies would be included in the overall pool of safety data. The Sponsor stated that these data would not initially be included with the NDA submission for reasons only associated with the dates these studies would conclude. It was further clarified that these data would be submitted as they become available and would be added to the pooled data as well as presented separately. The Agency also requested that all safety data be grouped by study phase in addition to being presented in pooled format, to which the Sponsor agreed.

The Agency emphasized that the Sponsor's intention to submit the data organized only by system organ class and by preferred terms was not acceptable, because grouping by MedDRA higher level terms (HLT or HLGT) is often more meaningful. Two-level tables would be more informative if grouping were done by SOC and HLGT, or by SOC and HLT. For many analyses, though, three-level MedDRA tables would be most appropriate (SOC, HLGT, PT). The Sponsor indicated that they would seek further discussion with the Agency on this issue to determine how best to organize the data for Agency evaluation during the review of the NDA.

The Sponsor inquired as to the specific format for the suggested thesaurus of terms. The Agency specified that a table in the electronic document providing shortcuts for the appropriate coding would be sufficient. If necessary to reach agreement, further discussion concerning the thesaurus would also be possible.

Question 5: Does the Division concur with our proposal regarding the presentation of narratives?

FDA RESPONSE:

- **While it is acceptable to provide narratives for only a subset of SAEs, further discussion is needed to determine which events would be of interest.**
- **Of ≈90 AEs listed in the 11/2004 spreadsheet, only three were flagged as narrative-worthy. Many of the non-serious AEs listed would appear to merit inclusion of narratives, such as ventricular arrhythmia, manic reaction, and pruritic maculopapular rash.**
- **We would like to ensure that the criteria for deciding which SAEs require narratives will provide us with the information we require, and also minimize the need for multiple additional information requests during the review.**
- **Narratives should be provided for all adverse events resulting in treatment discontinuation, regardless of causality assessment.**

The Sponsor stated that narratives would be provided for all SAEs. Given the relatively small number of SAEs, the most straightforward approach would be to provide narratives for all of them.

Question 6: Does the Division agree that this pediatric proposal is acceptable?

FDA RESPONSE

- We agree that a waiver can be granted for pediatric studies in children under age 12.
- We also agree that studies in children ages 12-16 can be deferred until after approval.
- A Proposed Pediatric Study Request should not be submitted until safety and efficacy in the adult population have been established (i.e., after approval).

Discussion:

The Agency noted that the pediatric population is defined as subjects 16 and under; therefore, the adolescent study should be conducted in patients aged 12-16.

Question 7: Does the Division concur with the proposals regarding the format of the electronic submission?

FDA RESPONSE

- Bear in mind that all requirements detailed in the US Code of Federal Regulations must be satisfied, either in addition to, or in lieu of CTD specifications

Question 8: Does the Division concur with our proposed data component for the electronic submission?

FDA RESPONSE

- Data from the 40-week extension phases of A3051007 and A3051016 should also be included (A3051018 and A3051019, respectively)
- Datasets for the Phase 1 studies should include all relevant safety information (AEs, disposition, etc.)
- CRFs should be provided for all SAEs of interest, not only for those categorized as treatment-related
- Please clarify what is meant by "subject data listings" to be provided in PDF format, and how this will differ from the case report tabulations to be submitted as SAS transport files.
- You have proposed to omit submission of some items the division would find helpful. Please submit a comprehensive list of investigators, providing enrollment and quit rate by site for the pivotal trials, and total enrollment for each investigator.

Compilation of this information from the various individual study reports is cumbersome for the reviewer and may introduce error.

- **A list of INDs would also be helpful**

Discussion:

The Agency emphasized the need for corresponding datasets (SAS Transport files). The study reports should be rendered (to PDF) as text with tables, rather than as images. Data listings in study appendices should also be rendered directly from source tables wherever possible, in order to facilitate preparation of written reviews.

Question 9: Based on the information presented in the Pre-NDA meeting package, is the proposed submission adequate for review?

FDA RESPONSE

- **As proposed your application would satisfy most Agency requirements**
- **It appears as if the overall patient exposure will be adequate, and the expected efficacy studies completed**
- **The application itself will be assessed for adequacy at the time of filing review**

Question 10: Does the Division concur with the proposed content of the Safety Update? In which module should the Update be located?

FDA RESPONSE

- **Submission of information on deaths and SAEs from ongoing studies at the 120-day safety update is acceptable.**
- **These should be integrated into the existing data in order to update all relevant safety tables**
 - **Exposure-by-duration, SAEs, TEAEs, subject disposition**
- **Modules 2 and 5 must be updated (clinical safety)**
- **Module 1 (regulatory documentation) must also be updated, and, if appropriate, the remaining modules**
- **Adequate links must be provided between Module 2 reports and Module 5 data**
- **For studies completed subsequent to database lock, complete final study reports should be submitted.**

Discussion:

The Sponsor inquired about the need to integrate the 120-day update data (with those from the initial submission). They expect there will only be 56 patients from single-dose studies to add to the safety database. It was agreed that further discussion on this subject could be necessary once

all data were available. The Agency wanted to evaluate these data before deciding whether integration, and submission of an updated safety database, would be warranted.

The Sponsor further clarified that they had no intent to enroll new patients. At this point, they were in the process of completing safety data collection.

Question 11: Does the Division concur that we have provided appropriate justification for the uses of the Minnesota Nicotine Withdrawal Scale (MNWS), Brief Questionnaire of Smoking Urges (QSU-Brief), and Modified Cigarette Questionnaire (mCE), also known as the Smoking Effects Inventory (SEI)?

FDA RESPONSE

- We have consulted our Study Endpoints and Label Development Team (SEALD response on following slide) to help assess the validity and relevance of your patient reported outcomes (PROs)
- Discussion of PROs from a battery of secondary outcome measures, in product labels and package inserts is discouraged

SEALD RESPONSE

- The information provided in the briefing was not sufficiently detailed to determine whether these instruments would be adequate to support statements in labeling or advertising.
 - Adequacy of the measures will depend in part on the statements you intend to make based on these assessments.
- For each instrument, please submit for our review detailed documentation of the research conducted to develop and validate it, and to determine and interpret scores
 - If multiple modes of administration (e.g., interviews, self-assessment questionnaires, electronic assessments, etc.), or multiple translations or cultural adaptations were used during the development of a given PRO, you will need to demonstrate that each version of the assessment produces valid, reliable, and comparable data for combined analysis.

Clinical

- Integrated Summary of Safety composite datasets should be provided, in their own folders
 - All AEs, all TEAEs, all SAEs, etc.
 - One record, or line, per event
- Dataset definition tables should include, for each field, a list (for categorical) or range (for numerical) of acceptable values
 - This information can be included in the 'Comments' column

Clinical

- Provide hyperlinks from the clinical table of contents, the tabular listing of clinical studies, and each dataset definition table, to the corresponding dataset folder
- Key ISS tables should hyperlink to the relevant CRFs
 - Deaths, TESAEs, discontinuations due to SAEs, etc.

- **Consider returning to demonstrate the submission for the primary reviewers**
 - **Ideally, this would occur once the NDA is nearly complete and ready for review, but prior to application**
 - **Clarifications, and if necessary, corrections, could be made before the “review clock” starts**

Discussion:

The Agency asked if the data would capture as a primary endpoint the continuous quit rate. The Sponsor indicated that the study would measure a continuous quit rate over 4-week period as an endpoint, i.e. not study drop-outs, but successful quitters.

The Sponsor indicated that they would submit a more detailed package for the SEALD group to evaluate. The Agency stated that they would provide a written response from the SEALD group, and determine then if there was a need for further discussions regarding PROs.

The Sponsor stated that they would plan to return when the application neared completion, in order to demonstrate navigation of the electronic submission and datasets and to solicit additional feedback.

The Sponsor also informed the Agency that the NDA would be submitted on November 15, 2005.

Final Statement of Understandings

1. The Sponsor will follow the Agency guidance document for preparation of the electronic datasets.
2. The Sponsor will provide in the submission a rationale for dosing in their clinical studies.
3. The Sponsor will consider ways to optimize presentation of safety data. MedDRA ‘High Level Group Terms’ would be utilized and three-level MedDRA tables presented where appropriate. Further discussion with the Agency could be necessary.
4. The Sponsor will provide a proposal for the study of pediatric patients in the range 12-16 years of age after establishing the safety of the drug in the adult population.
5. The Sponsor will submit narrative reports of all serious adverse events (SAEs). These will include study drug dose and duration of use, and also report patients’ smoking status.
6. The Sponsor will provide a list of all investigators as part of Module 1 and a list of all clinical studies in Module 2.
7. The Sponsor will submit all relevant information for the chosen PRO instruments, as outlined above. Label claims based upon PRO data might warrant discussion with the Agency at a later time.

(Meeting minutes prepared by Dominic Chiapperino, Ph.D., Regulatory Project Manager)

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

/s/

Dominic Chiapperino
12/29/2005 01:38:34 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21,928

NDA ACKNOWLEDGMENT

Pfizer Inc.
50 Pequot Avenue
New London, CT 06320

12-16-05

Attention: Michael Page
Director, Worldwide Regulatory Affairs
Pfizer Global Research & Development

Dear Mr. Page:

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: Champix (varenicline tartrate) Tablets, 0.5 mg and 1 mg

Review Priority Classification: Priority (P)

Date of Application: November 9, 2005

Date of Receipt: November 10, 2005

Our Reference Number: NDA 21-928

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 January 9, 2006, or sixty days from the date payment is received in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be May 10, 2006.

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.

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. We reference the deferral granted on June 9, 2005, for the pediatric study requirement for this application.

NDA 21-928

Page 2

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 Anesthesia, Analgesia, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions me at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

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

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/s/

Parinda Jani
12/16/2005 12:31:17 PM
for Dominic Chiapperino

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>	
TO (Office/Division): Controlled Substance Staff, HFD-009 Attn: Corinne Moody Michael Klein Katherine Bonson			FROM (Name, Office/Division, and Phone Number of Requestor): Dominic Chiapperino, Regulatory Project Manager Division of Anesthesia, Analgesia, and Rheumatology Products Contact: 301-796-1183, chiapperinod@cder.fda.gov	
DATE 12-14-05	IND NO.	NDA NO. NDA 21-928	TYPE OF DOCUMENT Original Submission NDA, eCTD format	DATE OF DOCUMENT November 10, 2005
NAME OF DRUG Varenicline Tartrate		PRIORITY CONSIDERATION Priority Review	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE ASAP for filing purposes
NAME OF FIRM: Pfizer Consumer Healthcare				
REASON FOR REQUEST I. GENERAL				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <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 </div> <div style="width: 33%;"> <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 </div> <div style="width: 33%;"> <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): </div> </div>				
II. BIOMETRICS				
<div style="display: flex;"> <div style="width: 50%;"> <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 <input type="checkbox"/> OTHER (SPECIFY BELOW): </div> <div style="width: 50%;"> <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): </div> </div>				
III. BIOPHARMACEUTICS				
<div style="display: flex;"> <div style="width: 50%;"> <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES </div> <div style="width: 50%;"> <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST </div> </div>				
IV. DRUG SAFETY				
<div style="display: flex;"> <div style="width: 50%;"> <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 </div> <div style="width: 50%;"> <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS </div> </div>				
V. SCIENTIFIC INVESTIGATIONS				
<div style="display: flex;"> <div style="width: 50%;"> <input type="checkbox"/> CLINICAL </div> <div style="width: 50%;"> <input type="checkbox"/> NONCLINICAL </div> </div>				
COMMENTS / SPECIAL INSTRUCTIONS: <p>Varenicline tartrate (NDA 21-982), a centrally acting new molecular entity, acts as a partial agonist at $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptors. The applicant has proposed the indication statement: "CHAMPIX is indicated for smoking cessation". We are granting priority review status, in which case the PDUFA goal (action) date would be May 10, 2006.</p> <p>Please review the application's abuse liability section. Of a more urgent nature, please review for any filing issues. This is an electronic submission in eCTD format. The submission is in the EDR.</p> <p>If you require additional information or analyses please let our Division know so that we may facilitate your request(s).</p>				

Thank you.

SIGNATURE OF REQUESTOR

Dominic Chiapperino, Ph.D. (electronic)

METHOD OF DELIVERY (Check one)

☒ DFS

☐ EMAIL

☐ MAIL

☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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On Original**

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

/s/

Dominic Chiapperino
12/15/2005 12:29:49 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

11-9-05

Pfizer Global Research and Development
Worldwide Regulatory Affairs
50 Pequot Avenue
New London, CT 06320

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

Dear Mr. Parker,

Please refer to the meeting between representatives of your firm and FDA on December 9, 2002. The meeting was an End-of-Phase 2 Meeting for CP-526,555 (IND 58,994).

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, please call me at 301-827-7416.

Sincerely,

Victoria Kao
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-928

10/25/05

Pfizer Inc
Attention: Mike Page, Director
50 Pequot Ave
New London, CT 06320

Dear Mr. Page:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Champix (varenicline tartarate) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on January 5, 2006. The purpose of the meeting was to discuss CMC issues, U

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

If you have any questions, call me, at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 28, 2005
TIME: 10:00 pm -11:30 pm
LOCATION: White Oak, Room 1309
TOPIC: Varenicline Tartrate
TYPE of MEETING: Type C
MEETING CHAIR: Moheb Nasr
MEETING RECORDER: Amy Bertha

FDA ATTENDEES:

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Moheb Nasr, Director
Chi-wan Chen, Deputy Directory
Guirag Poochikian, Associate Director of Regulatory Science & Policy
John Simmons, Director, Division of Pre-Marketing Assessment III
Ravi Harapanhalli, Branch Chief, Division of Pre-Marketing Assessment III
Ying Wang, Chemist, Division of Manufacturing Sciences
Steve Miller, Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment II
Amy Bertha, Regulatory Health Project Manager

OFFICE OF COMPLIANCE, DIVISION OF MANUFACTURING AND PRODUCT QUALITY

John Dietrick, Team Leader
Kris Evans, Sr. Reg. Operations (Attended via teleconference)
Zi Qiang Gu, Consumer Safety Officer

OFFICE OF REGULATORY AFFAIRS, DIVISION OF FIELD INVESTIGATIONS

Bob Coleman, Consumer Safety Officer (Attended via teleconference)

OFFICE OF NEW DRUGS

Rigo Roca, Deputy Director

PFIZER ATTENDEES:

Jeff Blumenstein, Global Head, Global Regulatory CMC/QA
Roger Nosal, Senior Director, Global Regulatory CMC
Tom Garcia, Associate Director, Global Regulatory CMC
Lana Liem-McDonnell, Director, Global Manufacturing Services
Frank Busch, Research Fellow, Chemical R&D
Mary am Ende, Associate Research Fellow, Pharmaceutical R&D
Tim Graul, Senior Principal Scientist, Analytical R&D
Mike Page, Director, Worldwide Regulatory Affairs
Chris Sinko, Senior Director, Analytical R&D

BACKGROUND:

This meeting is a follow-up to the April 19, 2005, June 15, 2005 and August 11, 2005 meetings
[] varenicline tartrate tablets (IND 58,994).
The NDA for varenicline tablets is expected to be submitted in November 2005. []
[] The purpose of this meeting was to []
[] The briefing package was received on October 11, 2005.

THE MEETING:

Chi-Wan Chen introduced the members of the CMC review team that will be responsible for reviewing the upcoming varenicline tartrate NDA: Ravi Harapanhalli (team lead), Steve Miller, and Ying Wang. Members from the Office of Compliance and Office of Regulatory Affairs were also present at the meeting and will be working closely with the Office of New Drug Quality Assessment [] Amy Bertha will be the CMC contact from the FDA [] and Tom Garcia will be the point of contact from Pfizer.

FDA asked Pfizer to clarify the definitions of the terms []

Pfizer went through an example []

Pfizer further clarified that if they do not know whether []
[] FDA raised concerns over []
[] Pfizer said
that, as more scientific data is generated and their scientific knowledge []
increases, []
[] Consequently, the
[] could be included in the specifications.

FDA asked how Pfizer determines whether []
[] Pfizer said that []

]]

Frank Busch from Pfizer presented an example of a drug substance []

from Pfizer presented an example of a drug product []
these two presentations are attached.

] Mary am Ende
] The slides from

CLOSING REMARKS AND NEXT STEPS:

The next meeting will take place after the CMC review team has made their initial assessment of the NDA. The purpose of this next meeting will be to ask clarifying questions and to discuss critical CMC issues identified []
]

Minutes Preparer:

For

Amy Bertha

Regulatory Project Manager

Office of New Drug Quality Assessment

Chair Concurrence:

Moheb Nasr

Director

Office of New Drug Quality Assessment

12 Page(s) Withheld

☒ § 552(b)(4) Trade Secret / Confidential

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(4) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 58,994

9/16/05

Pfizer Global Research & Development
Attention: Mike Page, Director,
Worldwide Regulatory Strategy
MS 8260-1608
Eastern Point Road
Groton, CT 06340

Dear Mr. Page:

Please refer to your Investigational New Drug Application (IND) 58,994 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for varenicline tartrate tablets. [

]

We also refer to the meeting between representatives of your firm and the FDA on October 28, 2005. The purpose of the meeting was to brief the CMC review team [

]

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 Amy Bertha, Regulatory Project Manager, at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
Regulatory Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Date/Time: August 18, 2005, 3:30 - 5:00 PM
Location: FDA, Parklawn Building, Conference Room "C"
Application: IND 58,994
Sponsor: Pfizer Inc.
Drug/Dosage Form: Varenicline Tartrate
Indication: Smoking cessation
Type of Meeting: Type B (Pre-NDA)
Meeting Chair: Celia Winchell M.D., Medical Team Leader, Addiction Products, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Minutes Recorder: Dominic Chiapperino, Ph.D., Regulatory Project Manager, DAARP

Meeting Attendees:

Pfizer	Title
Reijo Salonen	Vice President, Neuroscience, Medical and Development Sciences
Mark Ammann	Senior Director, Psychiatry, Worldwide Regulatory Strategy
Mike Page	Director, Worldwide Regulatory Strategy
Ed Harrigan	Senior Vice President, Worldwide Regulatory Affairs & Quality Assurance
Doug Feltner	Senior Director, Neuroscience, Medical and Development Sciences
Mohan Beltangady	Vice President, Global Head, Statistics
[redacted] (by phone)	[redacted]
FDA	Title
Rigoberto Roca, M.D.	Deputy Division Director, DAARP
Celia Winchell, M.D.	Medical Team Leader, Addiction Products, DAARP
Thomas J. Permutt, Ph.D.	Team Leader, Statistics
Howard Josefberg, M.D.	Medical Officer, DAARP
Pratibha Rana	Regulatory Project Manager, DAARP
Michael Klein, Ph.D.	Team Leader, Controlled Substance Staff (CSS)
Katherine Bonson, Ph.D.	Pharmacologist, CSS
Corinne P. Moody	Science Policy Analyst, CSS
Yi Tsong, Ph.D.	Mathematical Statistician
Ling Chen, Ph.D.	Mathematical Statistician
Dominic Chiapperino, Ph.D.	Regulatory Project Manager, DAARP

Meeting Objective(s): The discussion of Pfizer's proposed statistical analysis plan for protocol 3019 in the determination of abuse liability.

General Discussion: Following minutes from the discussion of the draft of Pfizer's questions that were included in the May 11, 2005 meeting, the large group discussion was presented below in

italicized text in the order in which they were addressed at the meeting. Agency responses, prepared prior to the meeting and presented on slides, are **bolded**. Discussion is presented in normal text.

Opening comments by Pfizer:

Pfizer stated that they desired this meeting based partly on their experiences with the Agency in determining abuse liability of another Pfizer drug, pregabalin. In that case, it was Pfizer's impression that there was little disagreement with the data collected, but that Pfizer and the Agency seemed to disagree on the conclusions that could be drawn from the data regarding whether pregabalin had abuse liability. Their goal regarding varenicline tartrate was to discuss their data analysis plan for the clinical study, A3051039 (hereafter, 1039), which is completed and now unblinded, and come to agreement with the Agency on how best to use the data to inform the judgment of abuse liability.

Opening comments by the Agency:

Dr. Klein stated that the Controlled Substance Staff (CSS) viewed the study in question, 1039, as only one part of the overall assessment of the relative abuse liability of varenicline tartrate. Specifically, he warned that focusing on one human abuse liability study loses sight of the big picture in assessing the relative abuse potential of any drug.

Dr. Katherine Bonson then delivered the CSS presentation
Abuse Liability Assessment

Controlled Substance Staff comments presented by:

- Katherine Bonson, Ph.D., Pharmacologist, CSS
- Michael Klein, Ph.D., Team Leader, CSS

The Abuse Potential Section of an NDA [21 CFR § 314.50 (5) (vii)] includes:

- **Proposal for scheduling and all scientific data that forms the basis of the proposal**
- **Abuse Potential Assessment:**
 - **Chemistry (including chemical similarity to other drugs of abuse)**
 - **Pharmacokinetics and pharmacodynamics**
 - **Primary data from abuse potential studies in animals and humans**
 - **Adverse events in clinical studies related to abuse potential**
 - **Integrated summaries of safety and efficacy (ISS and ISE)**
 - **Information related to overdose**
 - **Prospective assessment of the incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies**
- **CSS evaluates all data submitted in the Abuse Potential Section of the NDA when determining the abuse liability of a new medication**
- **Positive and negative data from all studies are weighed during the review process.**
- **Human laboratory abuse liability study data are approached in a manner similar to safety data.**

- **Individual responses are evaluated, in addition to statistical averages and standard deviations of data gathered from all study participants. Data are evaluated qualitatively, as well as quantitatively.**

Discussion:

Pfizer raised an objection to the third bullet item likening abuse liability study data to safety data. Their position was that safety data pertained to conditions where there were objective assessments. Dr. Klein responded that the abuse liability evaluation is considered part of the safety assessment for a new drug; the evaluation of abuse potential encompasses a number of measurements that attempt to predict the likelihood of abuse and resulting public health risks that may result from abuse of the new drug. Abuse liability measures are inherently subjective assessments. Pfizer believes that it is not currently known what circumstances or outcomes are relevant in determining abuse liability of a study drug.

Dr. Bonson replied that the Agency evaluates drugs on the basis of two factors: safety and efficacy; that abuse liability is part of the safety assessment. Regarding the issue of assessment of "subjective responses," Dr. Bonson stated that there is a 40 year history in developing the inventories used to assess abuse liability in humans. The instruments utilizing subjective measures have been repeatedly validated using known drugs of abuse, and the overall methods used to assess abuse liability have recently been confirmed in the medical literature by a leading scientific organization dedicated to study and research in drug abuse. CSS uses this same methodology as part of the abuse liability assessment consistently, whether applied to known drugs of abuse or new molecular entities, which ranges from chemistry to animal behavior to epidemiology, and thus is not predominantly subjective.

Pfizer stated that in the case of pain, it was clear what it meant when a pain measurement was reduced by a drug under development, but this was not the case with abuse liability assessments. Dr. Bonson replied that when there was a reduced score in a subjective pain assessment, this was exactly analogous to an increased score in the subjective assessments of validated scales. Relative abuse potential is assessed. The correct and appropriate positive control needs to be selected in order to make the "relative" assessment of abuse potential.

Pfizer stated that many individuals experience a drug but don't abuse it, though some do, so it is difficult to know how to interpret human abuse liability studies. Dr. Bonson responded that the frequency of use of a drug is not the sole standard in determining abuse liability. Other factors, as required in the Abuse Liability Section of the NDA, are also evaluated. However, in the interest of public health and safety, drugs that produce positive subjective states are scheduled under the Controlled Substances Act, if they meet the criteria for scheduling.

Thus, Dr. Bonson noted that this is why individual responses within a human abuse liability study are of interest to the Agency, even if the overall mean showed no statistically significant difference from placebo. Dr. Klein concurred, and stated that this is why abuse liability assessments are part of the overall safety evaluation for the drug. He added, however, that the measures in typical abuse liability studies are surrogates used to be predictive of whether a drug might be abused.

Pfizer maintained that there were no specific hypotheses to test in conducting abuse liability studies. Dr. Tsong stated that there are three hypotheses that could be tested: 1) to establish if the population tested is valid; 2) to show that there were significant differences between the

study drug and known abusable drugs; and 3) to show that there is not much of a difference between the study drug and placebo.

Pfizer expressed their concerns that, like with their drug, pregabalin, there were no fixed rules or common understandings of outcomes in planning and conducting abuse liability studies. This was of particular concern to them given that that 30% of their portfolio are drugs with CNS activity. [] consultant to Pfizer, stated that they tried to put forward a plan that would put confidence intervals around various observed effects in the study, and that they sought to achieve maximum power with their study. Exploratory analyses could be very detailed and far reaching, but prospectively planned analyses state the objectives of the analysis at the outset.

The discussion on this slide was then concluded in the interests of time.

Study Objectives: To predict the likelihood of drug liking and the potential for abuse.

CSS' approach to review of abuse liability studies includes:

- **Is the study conducted appropriately?**
- **Is the appropriate population studied?**
- **Is an appropriate positive control selected?**
- **Are the right doses of the test drug and positive control being studied in terms of abuse potential and safety?**
- **Are the appropriate outcome measures selected?**
- **Does the study have adequate statistical power?**

Regarding the human laboratory abuse potential study conducted with varenicline:

- **The study is designed adequately to determine whether varenicline has an abuse liability that is similar to amphetamine, the Schedule II drug selected as the positive control.**
- **The study does not utilize a positive control drug in a lower CSA schedule. Thus, it will be difficult to determine if varenicline has an abuse potential similar to or less than drugs in Schedule III, IV or V.**

Discussion:

[] asked if both doses of the positive control, amphetamine, are considered to be Schedule II drugs. He wanted to know if the lower dose might serve as a positive control for Schedules III, IV, or V drugs since it would produce less positive responses than the higher dose. Dr. Bonson replied that substances, not doses of the substances, were scheduled under the CSA, unless they were in a specific drug combination with another drug that would be considered likely to reduce the abuse potential of the drug under review. Thus, when a Schedule II drug of any dose is used as the positive control, the only conclusion that can be drawn is whether the test drug has an abuse liability similar to a Schedule II drug, but not whether it is similar to a drug in Schedules III, IV or V. She additionally reminded Pfizer that it was their decision to use amphetamine as the positive control, after the Agency had suggested the use of phentermine, a Schedule IV drug as the positive control. Dr. Klein then reiterated that this single human abuse liability study will be only one of many studies that will determine our recommendation for scheduling status.

Outcome Measures:

- Selected subjective assessments of abuse liability are acceptable.
- Each of the subjected assessments measure different facets of abuse liability.
- However, the measures have only been validated individually, not when combined together into one measure.

In conclusion:

- Abuse liability relies upon all primary data submitted in an NDA, which include chemistry, binding, preclinical behavioral studies, human laboratory abuse liability studies, adverse events in clinical safety/efficacy studies, and epidemiology (if available).
- No single study determines the abuse liability of a drug or whether a drug will be recommended for scheduling.

Discussion:

At the end of the CSS presentation, Pfizer and the Agency began a general discussion on the merits of multivariate endpoint analysis and/or composite endpoints versus a minimal number of primary endpoints. Pfizer expressed concerns that the criteria for determining abuse liability could not be trusted to accurately judge the degree of abuse liability for a given drug. Dr. Tsong stated that with multiple endpoints to consider, the burden of determining that the drug would not likely be abused would be greater, as every hurdle established in the study would have to be cleared. A single composite endpoint would be reasonable as an alternative, but none have been proposed thus far that have been validated to assess abuse liability. Dr. Tsong stated that only validated endpoints will be used to determine whether varenicline shows an abuse liability signal in the human study.

Dr. Chen stated that the statistical evaluation of the human abuse liability study is similar to an efficacy study where all co-primary endpoints need to show efficacy individually. Analysis of multiple co-primary endpoints is a difficult task because the power of such studies is usually low. Dr. Chen also reminded Pfizer that there is a Multiple Endpoints Expert Team in Pharmaceutical Research and Manufacturers of America who are doing research in this area. However, no concrete solution for this problem has been proposed from the Team yet. Pfizer stated that they were aware of this.

Pfizer pointed out the need for validation of measures that assess abuse liability. Since assessing abuse liability is a common concern for sponsors of CNS-active drugs, Pfizer expressed the view that concerned companies may wish to pool research efforts to see if patterns or methods emerge from various studies that would indicate an effective measure for determining abuse liability. They noted that the Agency's Critical Path Initiative specifically mentions abuse liability assessment as one of the projects, and that a cooperative effort among various companies concerned with abuse liability assessment needs to be coordinated.

Questions: Abuse Liability

Statistical comments presented by

- Ling Chen, Ph.D. Mathematical Sciences Division, Acting Deputy Director
- Yi Tsong, Ph.D. Mathematical Sciences Division, Acting Deputy Director

Question 1. Does the Agency agree that the proposed revisions to the analysis plan for Protocol A3051039 are appropriate to facilitate the evaluation of physiologic, subjective and reinforcing effects of varenicline compared to amphetamine and placebo? Specifically:

- Assessment of peak effects rather than peak and mean effects of VAS Drug Liking and Drug High Scores and ARCI Abuse Potential Subscale measured multiple times during the 8 hours post dose.*
- Analysis of the four endpoints using a mixed effects model for a multivariate outcome (Attachment 2, Analysis 1).*
- Combination of the four endpoints in a composite endpoint (Attachment 2, Analysis 2).*

FDA Response:

Endpoint Analysis

- We agree with assessment of peak effects of primary endpoints during the 8 hours after drug administration.**
- We do not support the use of multivariate analysis for this study since multivariate analysis is not appropriate for drug abuse potential studies. This case is similar to the efficacy study where all co-primary endpoints need to show efficacy individually.**
- We do not support the use of a composite endpoint, since the four co-primary endpoints measure different aspects of abuse liability.**

Discussion:

The second bullet item elicited much discussion in which Pfizer questioned the Agency's position that multivariate analysis could not be helpful in assessing abuse liability. [REDACTED] presented Pfizer's position that multivariate tests involving various components or combinations of components could provide a scientifically sound method.

Dr. Chen stated that univariate analysis for each co-primary endpoint was a preferred method of analysis, to which [REDACTED] requested a more detailed explanation of the Agency's ideas. He asked if the Agency wanted each endpoint tested separately against placebo, and if so, what the goal was in testing each separately. Should, for example, all four endpoints show statistically significant differences between the study drug and placebo or a positive control?

Dr. Bonson stated that the Multiple Choice Procedure, one of the four measures chosen by Pfizer for the multivariate analysis, is known to the Agency not to have been validated when tested against scheduled drugs of abuse. Therefore, its proposed use in multivariate analysis is of questionable value. Dr. Bonson additionally restated that merging selected endpoints from the ARCI, VAS and MCP has not been done previously and is not validated as a method for evaluating human laboratory abuse liability studies.

Dr. Tsong expressed that perhaps a multivariate use of the four tests could give a validated result, and one could then consider the four tests separately and see which gives a valid or close to valid result.

Dr. Tom Permutt explained that the problem is fundamentally one of multivariate analysis, in which the three important categories were measures between: 1) the positive control and the placebo; 2) the positive control and the study drug; and 3) the study drug and placebo. The validation step is not important by itself. The important point is that the study drug is studied using methods in which the positive control shows a statistically significant difference from placebo.

It was also explained to Dr. Tsong that using multivariate analysis instead of univariate analysis could provide a more powerful testing of the difference between treatments and avoid the p value adjustment for multiple endpoints. (In this case, for testing the 4 endpoints, the analysis becomes more stringent with type I error rate reduced to $\alpha = 0.05/4 = 0.0125$.) Dr. Tsong explained that through testing with individual endpoints, only the validated endpoints will be used in the analysis of test treatment.

Dr. Chen inquired about Agency thinking regarding the use of non-inferiority hypothesis testing to show that the test treatment is not statistically different from placebo. Dr. Chen explained that it can be achieved by showing that the mean response of the test treatment is no more than double the mean response of placebo.

Dr. Winchell asked Pfizer and the Agency statisticians whether they were only using a group mean analysis, since CSS had stated that they also evaluate individual outcomes for signals of abuse liability. Dr. Tsong indicated that Pfizer could analyze how many of the individual outcomes showed the result of "double the mean of placebo."

Dr. Tsong commented that twice the mean of placebo may be too stringent. In order to show that the mean of test treatment is less than the double of placebo mean, 1,000 patients may be needed for the study.

Dr. Tsong said it is still a working margin. In fact, many studies were shown to be invalid because they failed to show that the positive control differentiated from placebo. However, using the working margin concept, some drugs passed all tests requested, including the comparison between the test treatment and placebo.

Pfizer and FDA had agreed during the above discussion to forego discussion of Agency responses to remaining questions in order to continue their focus on the above issues. No time remained for discussion of responses in the meeting slides below.

Sample Size

- The sample size for each group was calculated by using the effect size observed between 20 mg amphetamine (a Schedule II drug) and placebo in an unpublished study. Stimulants in Schedule II have greater abuse liability than stimulants in Schedules III or IV, when compared with placebo.

- A sample size of 20 per group for two separate studies does not ensure even 80% power for most tests planned in these studies. In other words, the statement, “A sample size of 20 subjects will provide at least 98% power to detect a standardized treatment difference ranging from 1.0 to 2.0 in one primary endpoint” is incorrect.
- We suggest that you consider combining “smoker” or “non-smoker” into one analysis, and include smoking status in the model. We also suggest that you report the subgroup analysis for smoking status regardless of the observed significance level of this term in the model.

Question 2. Does the Agency agree that a determination of the validity of the study should be made on the basis of a statistically significant difference between amphetamine 30 mg and placebo for Analysis 1 and Analysis 2?

FDA Response:

- Yes, validity of the study can be shown by a statistically significant difference between amphetamine (as the positive control) and placebo.
- However, both doses of amphetamine should be compared with placebo. If both doses have statistically significantly higher mean response than placebo, then all doses of varenicline should be compared with both doses of amphetamine.

Question 3. Does the Agency agree that no statistically significant difference between varenicline and placebo for Analysis 1 and Analysis 2 would infer an absence of physiologic, subjective and reinforcing effects for varenicline in this study?

FDA Response:

- The answer is NO. “No statistically significant difference” does not mean “statistically significantly no difference”.
- By choosing to use a Schedule II drug (amphetamine) as the positive control (which the subjects receive prior to varenicline administration), there is a bias towards detecting subjective responses that are similar to those of a drug with high abuse liability.
- However, this design also produces a bias against adequately detecting subjective responses that are less than those produced by a Schedule II drug, but are produced by a Schedule III or IV drug.
- If the study results show that varenicline produces less rewarding effects than amphetamine, a Schedule II drug, it does not necessarily mean that varenicline has no abuse liability. It is possible that varenicline has an abuse liability consistent with a Schedule III or Schedule IV drug. This is true even if varenicline does not show a statistically significant difference from placebo.

- Without the use of a Schedule III or IV stimulant in the trial as a comparator, it is not possible to determine whether an insignificant difference between placebo and varenicline may be simply due to subjects assessing that varenicline does not have the same rewarding effects as the Schedule II comparator, amphetamine.
- Thus, if the data show that varenicline produces less rewarding effects than amphetamine, but similar or even less rewarding effects compared to placebo, it can only be concluded that varenicline has less abuse liability than a Schedule II drug, not that it has no abuse liability.
- This limitation is compounded by the small sample size which limits the power of the study.

Question 4. Does the Agency agree with the proposal to analyze each endpoint individually only if Analysis 1 or Analysis 2 shows a statistically significant difference to placebo?

FDA Response:

- The answer is NO.
- We suggest univariate analyses for each co-primary endpoint.

Discussion:

The issues raised by Question 4 were discussed (as recorded above) in a manner similar to the Agency's response to Question 1.

Final comments:

With little time remaining, Pfizer and the Agency agreed that the meeting had been very valuable. Both sides appreciated the efforts in preparation and the productive discussion of the various methods of analysis for determining abuse liability.

Meeting minutes were drafted by Dominic Chiappierino, Ph.D., Regulatory Project Manager, DAARP, and finalized by the Controller of Data Management.

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

/s/

Dominic Chiapperino
9/16/2005 03:52:17 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

8/16/05

IND 58,994

Pfizer Inc.
50 Pequot Avenue
New London, CT 06320

Attention: Mike Page
Director, Worldwide Regulatory Affairs
Pfizer Global Research & Development

Dear Mr. Page:

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

We also refer to your amendment dated June 20, 2005 (serial # 0150), containing a revised proposal for the provision of inclusion of MedDRA terms in your forthcoming NDA submission.

We have completed the clinical review of your submission and have the following comments and recommendations.

1. In our experience, MedDRA two-level tables (PT + SOC) contain too many individual Preferred Terms to allow for meaningful interpretation. Three-level tables should be presented (SOC, HLGT and PT) for the integrated summary, as well as for individual study reports. Tables without preferred terms need not include severity data.
2. All MedDRA AE datasets (integrated and also individual study) should be submitted with the NDA. These should include verbatim term and all five MedDRA levels (LLT, PT, HLT, HLGT, SOC).
3. Your proposal for the Phase I datasets is acceptable. These individual protocol-specific datasets should utilize identical file structure wherever possible, though. Specifically, demographic, disposition and AE datasets should contain identical column headings.

If you have any questions, call Dominic Chiapperino, Regulatory Project Manager, at (301) 827-1620.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Rigoberto Roca
8/16/2005 05:45:02 PM
for Bob Rappaport, M.D.

1-27-03



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 58,994

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

Attention: Mike Page
Associate Director I
Regulatory Strategy, Policy, and Registration

Dear Mr. Page:

Please refer to the meeting between representatives of your firm and FDA on October 9, 2003. The purpose of the meeting was to discuss chemistry, manufacturing, and control program to support an NDA for varenicline immediate release.

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

If you have any questions, call me at (301) 827-7431.

Sincerely,

{See appended electronic signature page}

Pratibha Rana, M.S.
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: December 9, 2002 **Time:** 4:00pm-5:00pm

Location: Parklawn Building, Potomac Conference Room

Sponsor: Pfizer Global and Research Development

Drug Name: CP-536,555 (IND 58,994)

Type of Meeting: End-of-Phase 2 (EOP2)

Meeting Chair: Celia Winchell M.D., Medical Team Leader

Minutes Recorder: Victoria Kao, Regulatory Project Manager

Pfizer	Title
Richard Anziano, MS	Biostatistics
Ilisa Bernstein, PharmD, JD	Regulatory Affairs
Andrew Clair, Ph.D	Regulatory Affairs
David J. Clark, MD	Clinical Sciences
Helene Faessel, Ph.D.	Clinical Sciences
Martin Finkelstein, Ph.D.	Drug Safety Evaluation
Michael Kronig, MD	Clinical Development
Scott Obach, Ph.D.	Drug Metabolism
Jonathon M. Parker, RPh, MS	Regulatory Affairs
Karen Reeves, MD	Clinical Development
Eric Watsky, MD	Clinical Development
FDA HFD-170	Title
Division of Anesthetic, Critical Care and Addiction Drug Products	
Bob Rappaport, M.D.	Division Director, Acting
Celia Winchell, M.D.	Medical Team Leader
Howard Josefberg, M.D.	Medical Reviewer
Dale Koble, Ph.D.	Chemistry Team Leader
Pat Maturu, Ph.D.	Chemistry Reviewer
Tim McGovern, Ph.D.	Supervisor, Pharmacology and Toxicology
Memata De, Ph.D.	Pharmacology and Toxicology Reviewer
Tom Permutt, Ph.D.	Statistics Team Leader
Dionne Price, Ph.D.	Statistics Reviewer
Suliman Alfayoumi, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
Victoria Kao, B.S.	Regulatory Project Manager
FDA	Title
Controlled Substance Staff	
Michael Klein, Ph.D.	Pharmacologist

Meeting Objective:

This was an End-of-Phase 2 (EOP2) meeting.

Background:

This was an EOP2 for CP-526,555, a selective acetylcholine receptor modulator in development for use in smoking cessation treatment in nicotine dependent subjects and for the maintenance of abstinence.

Three studies were conducted for Phase 2 program: A3051002, A3051007, and A3051016. All aimed to demonstrate efficacy compared with placebo.

The Sponsor proposes in Phase 3 to conduct a comparison study (A3051028) with Zyban® (bupropion SR) and placebo to demonstrate statistical superiority over Zyban (only Zyban-naïve subjects will be enrolled). The study will be supplemented by a post-hoc analysis of Zyban-naïve subjects in study A3051002. In addition, a maintenance study (A305mmmm) is planned.

The Sponsor requests feedback, as guided by questions submitted in background package dated November 7, 2002, on completed Phase 2 studies and designs of proposed Phase 3 studies.

MINUTES:

Following introductions, the discussion moved to questions the sponsor posed in the meeting briefing package dated November 7, 2002.

Chemistry, Manufacturing and Controls (CMC) Information and Questions

The background package contained no CMC issues to be discussed. The Sponsor confirmed that a separate CMC meeting will be requested at a later date.

Nonclinical Pharmacology and Toxicology

Question 11

Does the division agree that our proposed plans in conjunction with completed studies are adequate to support NDA approval from a Pharm/Tox point of view?

FDA Response:

- In general yes
- In absence of any demonstrated systemic toxicity in monkey, characterization of systemic toxicity profile should be performed in a short term study (4wks)
- Use of another route of administration may be necessary
- Demonstration that MTD/MFD has been achieved may be acceptable

Does the Division agree that the carcinogenicity results are not needed at the time of filing to support approval of the initial indication that involves a treatment duration of 12 weeks or less?

FDA Response:

Carcinogenicity studies should be submitted with the NDA as the expected clinical use may exceed 3-6 months duration.

Additional Pharm/Tox Comments

Safety qualification needed for impurities exceeding ICH recommendations.

Pharmacology/Toxicology Discussion

The absence of systemic toxicity in monkeys was thought to necessitate an additional study to obtain this information – potentially via another route of administration. The Sponsor clarified the maximum tolerated dose was achieved in the monkey and this was duplicated in IV studies. The Agency requested that the justification to support this position be submitted.

Human Pharmacokinetics and Bioavailability

There were no comments.

Controlled Substance

Question 9

Does the Division agree that these data, confirmed by subsequent data from clinical safety and efficacy studies, are consistent with labeling that CP-526,555 has low abuse potential without the need to perform a specific clinical abuse potential study?"

FDA Response

- Primary data from abuse potential studies for all NME's are needed for review, including: biochemical binding, self-administration, discrimination studies, and clinical studies A2051002 and A3051016. Final data and safety analysis from clinical study A3051016 will be assessed when the study is completed and submitted.
- Additional data are needed to support the claim that CP-526,555 has a low abuse potential. We need to determine *relative* abuse potential.
- Additional data are needed from clinical & preclinical studies that prospectively investigate the abuse potential of CP-526,555.

Additional Studies Recommended:

- A drug discrimination study in which animals are trained to low doses of a scheduled stimulant (such as amphetamine or methylphenidate), followed by CP-526,555 challenge sessions.
- A self-administration study in animals in which a wide range of doses of CP-526,555 are tested and compared against a scheduled stimulant.
- A study in animals that assesses whether repeated administration of CP-526,555 produces tolerance or physical dependence.
- Primary data from the diaries kept by subjects during the clinical studies. Self-reports may provide information about experiences with CP-526,555 that reflect abuse potential.
- A clinical study that prospectively assesses whether CP-526,555 induces positive subjective effects in a subject population of experienced drug abusers.

Abuse Potential

- The Sponsor should submit results and primary data from completed studies in the abuse potential section in the NDA, per the requirements of 21 CFR 314.50(5)(vii).

Controlled Substance Discussion

The Agency suggested that Sponsor conduct additional non-clinical studies (e.g., tolerance/physical dependence studies) and clinical abuse potential study. For CP-526,555, a Schedule IV drug such as phentermine might be an appropriate comparator. The suggested clinical study design was a dose ranging study in recent or current stimulant users/abusers who are not physically dependent on any drugs. The Sponsor was encouraged to submit the study protocols to Controlled Substance Staff (CSS) for review.

The Sponsor asked for the reasoning behind the Agency's request of a clinical study; it was pointed out that data from A3051002 and A3051016 showed a lack of abuse potential in multiple dose trials. The Agency responded that those studies did not focus on abuse potential. In addition, other questions related to dysphoria need to be addressed; an example would be when and at what percent frequency do nausea and vomiting occur.

However both sides acknowledged that CSS did not have enough data to make a full assessment. Consideration of a waiver of the clinical study would require full submission of existing primary data and rationale by the Sponsor.

Clinical

Question 1

Will these studies (as outlined in background package dated November 7, 2002) suffice as pivotal trials for this indication in an NDA application?

FDA Response

Yes, given efficacy findings consistent with those from your Phase 2 studies and adequate safety data, the proposed trials should suffice for the indication of smoking cessation.

Question 2

Does the Agency agree that one additional trial coupled with the evidence from the A3051002 trial will form an adequate basis for textual and tabular inclusion of CP-526,555's replicated superiority over Zyban in the Clinical Trials section of the label?

FDA Response

- Your revised results (previous Zyban® users excluded) from study A3051002 do not achieve statistical significance.
- Superiority to Zyban® must be demonstrated, in two adequate and well controlled clinical trials in which Zyban® is used according to labeled directions.
 - Proposed use of Zyban in protocol A3051028 deviates from Zyban label instructions.

Question 3

Assuming CP-526,555 demonstrates statistical significance over placebo at the 24-week time point, does the Agency agree that this study alone would be a basis for:

- An indication for the long-term maintenance of abstinence?
- Inclusion of information on long-term maintenance of smoking cessation in the Clinical Trials and Dosage and Administration sections?

FDA Response

- An indication for "Long-Term Maintenance" implies to clinicians and patients that the medication is for long-term use, that is, for an indefinite duration.
- For true long-term maintenance use your efficacy trials and follow-up periods would need to reflect long-term use, as would your safety database.
- Description of longer term use as supported in your planned study A305mmmm may be included in your D & A section.

Question 4

Will the planned safety database achieve the Agency requirements for approval with regard to the numbers of subjects, the doses, and the duration of exposure?

- Despite the fact that CP-526,555 will be labeled for use for a predefined time period, 12 or 24 weeks, we believe that clinicians will prescribe the drug chronically.
- The anticipated safety database appears to have sufficient short term exposure at 1 mg BID.
 - Note that dose-by-duration tables must reflect actual duration of exposure, not the duration of the trial.
- Ensure that you have at least 300 patients treated for six months and 100 treated for one year, consistent with ICH guidelines.
- As proposed, this safety database would not allow for an indication [

]

Question 5

Does the Agency agree that all four endpoints, which differ in their stringency, are all informative to prescribers and consequently merit inclusion in the labeling?

FDA Response

- The 4-week CQR for the last 4 weeks of treatment
 - Acceptable for shorter treatment courses.
 - Loses relevance as treatment period lengthens (Wks 20-24 vs. Wks 9-12).
 - May be used for study A3051028 (12 week treatment period) but not appropriate for A305mmmm.
- Long-term quit rate (Quit by end of treatment and ≤ 6 lapsed days during nontreatment followup)
 - This is an appropriate measure of long-term efficacy but necessitates collection of appropriate day-by-day smoking data (addressed with answer # 12).
- Continuous abstinence rate from beginning of last 4 weeks of treatment
 - Why measure only from the last 4 weeks? This allows for a long grace period.
- 7-day point prevalence is not informative

Question 6

Does the Agency agree that, if the data support clinical efficacy for these symptomatic endpoints, the drug may be labeled for these symptoms?

FDA Response

- Claims such as “reduced craving” and “reduced smoking satisfaction” are primarily labeling concerns.
- If your measurement instruments are valid and the purported differences clinically relevant evidence in support of such claims will be reviewed along with other labeling, marketing and promotional materials.
- Please justify your choice of instruments by providing articles and readings demonstrating validity, reliability, etc., for each.

Question 7

Does the Agency agree that this plan for pediatric development of CP-526,555 is acceptable and would be appropriate for a Written Request?

FDA Response

- In addition to pharmacokinetic and safety information in the relevant pediatric age groups, efficacy data is needed to support a smoking cessation indication in this population. The Agency’s position is that it is not possible to extrapolate efficacy data on smoking cessation in adults to support an indication of smoking cessation in the pediatric population.

- In our view the main task of the development program for smoking cessation in children, is to develop a method of identifying pediatric patients who have the same disorder seen in adults (tobacco addiction).
- We believe that a single efficacy study, along with confirmatory evidence from other sources, such as adult efficacy data, would suffice.
- Pharmacokinetic characteristics of nicotine metabolism, and measurement of exhaled CO in adolescents may differ from that in adults as well.

Question 8

Would the Agency agree to a broader CP-526,555 indication in labeling, namely one that includes
[]

FDA Response

To date, your clinical evaluations and development plan have focused on cigarette smoking cessation exclusively. In fact, several of your protocols exclude subjects that use other forms of tobacco. For the broader indication, efficacy of CP-526,555 in a heterogeneous [] population would need to be demonstrated in adequate and well controlled clinical trials.

- Cigarette smoke contains substances other [] that may, or may not contribute to addiction. Furthermore, the behaviors involved in smoking, chewing, or otherwise ingesting tobacco products are part of the habit, or the addiction, and do differ from route to route.

Question 10

Does the Agency agree that a single screening and baseline ECG (rather than in triplicate) in any subsequent trials will be adequate screening with regard to ECG monitoring?

FDA Response

- Increasing the number of baseline ECGs provides more data (beats per minute) to estimate the “true” baseline QT_c, and also from which to estimate each individual’s QT-heart rate relationship.
- Early safety signal recognition is exceedingly important
- As the number of drugs, some in use for years, discovered to possess potentially deadly cardiac conduction effects increases, so does the Agency’s vigilance with respect to this particular toxicity.
- Although there is no Agency wide requirement for triplicate ECGs (at this time), the stronger your safety evidence, the greater our level of comfort.
- All pre-dose ECG’s may be considered to be baseline. That is, ECG from screening and pre-dose ECG on Day 1 may each be considered as baseline ECG’s.

Question 12

Any Additional Concerns?

- Your proposal to define failure in long-term observations as smoking on 6 or more days over the observation period raises issues related to data acquisition

- Once monthly subject recollection for your data acquisition is likely to contribute a false sense of precision to your findings.
- You may want to consider a daily patient diary (paper or electronic), an interactive voice response system, or some other means of capturing behavior more contemporaneously, and more frequently.
- Measures which require a subject to recall any use vs. no use require less precision than those which are based on counting specific numbers of cigarettes or days of use over a recalled period of time.

Labeling and Use: Proposed Language

- [
-
- Only regimens for which there are replicated findings will be represented in labeling (e.g. 0.5 mg b.i.d. is not replicated)

Clinical Discussion

- 1) The Agency noted that efficacy with the 0.5 mg BID dose had not been replicated and therefore recommended that an additional study (or arm) with the 0.5 mg BID titrated dose be conducted for a label claim. After further clarification of A3051002 from the Sponsor, the Agency agreed to consider whether the 1.0 mg QD dose could be considered. The Division agreed to discuss this issue further internally and subsequently to conduct a teleconference with the Sponsor at a later date.
- 2) The Agency indicated that since study A3051002 can not be used to justify CP526,555's superiority over Zyban, two comparator studies validating such will need to be conducted. Sponsor's proposed A3051028, if modified so that Zyban's used according to its label, could qualify as one of the two. The second study would need to be at least 7 weeks in duration.

The Agency stressed that the bar for any superiority claim would be high. Clinically meaningful superiority was clarified as not just significance at a single endpoint, but would require success at multiple endpoints for efficacy and appropriate safety. The Agency mentioned that draft guidance is in development and may be issued in the near future.

The Sponsor sought to clarify how a superiority claim might translate into labeling. Tabular presentation with p-values may not necessarily be included in the label; a textual description may be an alternative. Were a table to be included, the Agency would exercise discretion over which endpoints can be included.

- 3) The Sponsor confirmed that CP-526,555 will not be labeled for one year administration and raised concerns regarding the large number of patients that would be need to be enrolled for the safety database to end with 100 patients at one year. The Agency agreed that if the Sponsor could provide rationale that the drug would not be used chronically (or intermittently for six months), it would be willing to reassess the one year requirement. Prescribing pattern for Zyban could help justify this position. Otherwise the data on 100 patients will need to be submitted at time of filing.
- 4) A 4-week CQR at the end of treatment would not be acceptable for the A305mmmm maintenance study; the grace period was too long to be acceptable for long-term therapy (the Sponsor suggested a

pharmacological basis for the long eight week grace period in study A3051028, a twelve week study). The Agency suggested that a measure of sustained response should be the primary outcome for Study A305mmmm.

- 5) If the scales are perceived to be valid and the data is clinically significant, then the Agency would consider including PROs in the label. Pfizer was asked to include the instruments, validation information and appropriate literature for this assessment. It was noted that a guidance document is being prepared with regard to PROs and may be issued within the next year.
- 6) The Agency agreed with the Sponsor agreed that a waiver for subjects under the age of 12 years would be appropriate. Furthermore, the deferral for obtaining pediatric information can be obtained after the submission of the NDA.
- 7) The Agency clarified that subject self recall of smoking would suffice for determination of abstinence but not for counts of occurrences of smoking.
- 8) A successful single dose, Phase I study would be acceptable for the claim that CP-526,555 is better tolerated when taken with food.

Minutes prepared by Victoria Kao 12/27/02

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

/s/

Celia Winchell
1/27/03 02:42:49 PM
for Bob A. Rappaport, M.D., Acting Division Director



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND: 58,994

11-6-03

Pfizer Global Research & Development
Worldwide Regulatory Affairs
50 Pequot Avenue
New London, CT 06320

Attention: Mike Page, B.Sc.
Director, Worldwide Regulatory Strategy
Worldwide Regulatory Affairs

Dear Mr. Page:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CP-526,555 (varenicline tartrate) 0.5 mg film-coated oral tablets.

We also refer to the meeting between representatives of your firm and the FDA on June 9, 2005. The purpose of the meeting was to discuss and agree upon the adequacy of clinical studies, and the requirements of an electronically submitted NDA in eCTD format.

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

If you have any questions, call me at (301) 796-1183.

Sincerely,

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

Enclosure

Industry Meeting Minutes

Date/Time: October 9, 2003 / 3:00 pm

Location: Parklawn, Conference Room C

Application: IND 58,994

Sponsor: Pfizer Global Research & Development

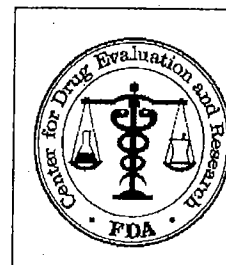
Drug Name: Varenicline Immediate Release

Indication: Nicotine Dependence

Type of Meeting: End of Phase 2

Meeting Chair: Dale Koble, Ph.D., Team Leader, Chemistry

Minutes Recorder: Pratibha Rana, M.S., Regulatory Project Manager



Pfizer Attendees	Title
Dorothy Beaulieu	Regulatory CMC
Stephane Caron	Varenicline Pharmaceutical Sciences Program Coordinator
Michael Cohen	Analytical Research & Development
David DeAntonis	Chemical Research & Development
Thomas Garcia	Pharmaceutical Research & Development
Roger Nosal	Director, Regulatory CMC Operations
Scott Obach	Pharmacokinetics, Dynamics and Metabolism
Mike Page	Worldwide Regulatory Affairs
FDA Attendees	Title
Bob Rappaport, M.D.	Director
Dale Koble, Ph.D.	Team Leader, Chemistry
Ravi Harpanhalli, Ph.D.	Chemistry Reviewer
Daniel Mellon, Ph.D.	Team Leader, Pharmacology/Toxicology
Mamata De, Ph.D.	Pharmacology/Toxicology Reviewer
Sue-Chih Lee, Ph.D.	Clinical Pharmacology Reviewer
Celia Winchell, M.D.	Team Leader, Addiction Drug Products
Howard Josefberg, M.D.	Medical Officer
Jila Boal, Ph.D.	Chemistry Reviewer
Sara Stradley, M.S.	Regulatory Project Manager
Pratibha Rana, M.S.	Regulatory Project Manager

Meeting Objective(s): The purpose of the meeting was to discuss the chemistry, manufacturing, and control program to support an NDA for varenicline immediate release.

General Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the September 10, 2003, meeting package. The slides containing the Sponsor's questions and Agency responses are presented below in italicized text. Discussion is presented in normal text.

CMC Questions

Question 1: Pfizer proposes that [] is controlled as a suitable regulatory starting material in the preparation of the drug substance. Does FDA concur with this approach?

FDA Response:

- *No.*
 - *Sufficiency of the information in the application for the Agency to evaluate the safety and quality of the drug substance.*
 - *Assurance that future changes in the manufacture of the starting material are unlikely to affect the safety and quality of the drug substance.*

Concerns on the Proposed Starting Material

- []

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-

-

- *Discussion point:*

]

Expectations of the Starting Material

- *Validated analytical method such as an HPLC for the starting material.*
- *Consistent acceptance criteria of NLT [] purity and specifications for the impurities.*
- *The proposed starting material, impurities in the proposed starting material, and the synthetic derivatives of the impurities in the proposed starting material should be not more than [] in the drug substance, if these are non-structural alerts for unusual toxicity such as genotoxicity*
- *If any of the above are structural alerts for genotoxicity, they should be limited to NMT [] in the drug substance.*
- *Alternatively, if the safety data is provided on the structural alerts indicating that they are not genotoxic, they should still be limited to NMT [] in the drug substance.*
- *All post approval changes should conform to BACPAC I.*

Discussion

The Sponsor stated that they have had adequate controls over the [] synthesis of varenicline and that the process was developed by them and that it is being transferred to the contract firms identified in the package. They felt that they have adequate controls in place with the proposed starting material. However, the CMC discipline raised an issue of potential genotoxicity [] in the synthesis of the currently proposed starting material. The requirements of safety assessment of genotoxic impurities were reiterated by the Pharm-Tox discipline.

Non Clinical Pharmacology/Toxicology Comment

- *Safety qualification of impurities exceeding ICH recommendations will be needed for an NDA submission.*
- *If any of the impurities has structural alerts for genotoxicity, specifications for this impurity in the drug product should be reduced to [] or adequate safety qualification should be provided.*
- *Qualification for genotoxic potential should include two in vitro genetic toxicology studies (point mutation assay and chromosomal aberration assay) with the isolated impurity tested up to the limit dose for each assay.*
- *Should this qualification produce positive results, the impurity specification should be set at [] Alternatively, the impurity may be assessed for carcinogenic potential in either a standard 2-year bioassay or an alternative transgenic mouse model.*

Discussion

The Sponsor stated that they have done a comprehensive evaluation [

] impurities. In []
they control the impurities to less than 10 ppm including the impurities containing
[] are impurities other than []

] The Sponsor also stated that they are planning a robust study to
control all structural alerts with potential genotoxicity at less than 10 ppm.

The Division questioned the level of regulatory control if []
defined as [] . The Division added that from a regulatory

perspective starting material should be defined []

The Sponsor stated that they are committed []

detailed impurity profile []

] The Division made it

clear []

] as the starting material provided it is []

] well characterized entity. The Division also stated that the Sponsor could make
any changes before the starting material as long as the changes conformed to
BACPAC I.

Question 2: While [] varenicline tartrate have been detected during
development, [] manufactured
[]

] under the recommended ICH temperature and stability conditions. Does
FDA concur with the Pfizer proposal to omit routine testing [] in varenicline
tartrate drug substance?

FDA Response:

- Additional data evaluation needed.

- Provide additional data []

] testing.

- Provide data to demonstrate clearly that the drug product safety, performance or
efficacy are not affected []

]]

- In the absence of the requested data, an acceptance criterion []
may have to be established for the drug substance to control bioavailability.]

[

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Discussion

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Question 3: Does FDA concur with Pfizer's assertion that, based on solubility, permeability and dissolution characteristics, varenicline tartrate IR tablets meet BCS I classification criteria and therefore qualify for a biowaiver?

FDA Response:

- *Additional data to support BCS Class I needed.*

Response from CMC and Biopharmaceutics

- *The drug is highly soluble and the drug product is rapidly dissolving. However, there are some reservations regarding the permeability of the drug:*
 - *To indicate that the bioavailability is — involves assumptions without validation. Strictly speaking, the confirmed bioavailability is [based on the data.*
 - *Provide additional data to support that the drug is highly permeable. E.g. in-vitro permeability study, comparative BA from iv and oral formulations, etc.*
 - *Note that the drug should be a non-narrow therapeutic index drug to be eligible for a biowaiver based on BCS Class I.*
-]

Discussion

The Division stated that the data does not confirm high permeability and ~ recovery. The Sponsor should provide data to support the additional claim of high permeability. The Division also informed the sponsor of several ways to support the BCS claim and that it can be supported with either *in vivo* or *in vitro* studies.

The Sponsor presented transparencies of individual data from a mass balance study, and agreed to provide additional data.

Question 4: Pfizer intends to adopt disintegration testing to evaluate drug product performance for commercial manufacture instead of dissolution testing. The solubility of varenicline tartrate tablets is so rapid that evaluation of dissolution in accordance with all USP conditions and criteria provides no meaningful assessment of product performance. Although a dissolution method has been developed, we believe that adequate assessment of drug product performance is achieved by disintegration testing. Does FDA concur with this proposal?

FDA Response:

- *This is a possibility and will be evaluated at the NDA.*

Disintegration versus Dissolution

- *Applicable for BCS Class 1 only (ICH Q6A DT 7)*
- *Additional requested data in support of the BCS Class I claim for the drug product.*
- *Pursuant to ICH Q6A (DT7), relationship should be demonstrated between disintegration and dissolution.*
- *Disintegration testing as discriminatory as the dissolution testing.*
- *Development information to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution vs. disintegration testing.*
- *Dissolution and disintegration testing for SUPAC changes and Disintegration testing alone for routine release and stability is a possibility.*
- *One regulatory method for dissolution and one for disintegration will have to be established.*
- *ICH Q6A definition of “rapidly dissolving” should be considered in the justification (dissolution — in 15 minutes at pH 1.2, 4.0 and 6.8).*
- *This criteria may have to be specified for the drug product.*
- *Actual data on disintegration is not provided in the package.*
- *Tighter disintegration and dissolution specifications may have to be proposed based on the disintegration-dissolution correlation studies only.*
- *Concerns about disintegration test’s discriminatory ability relative to dissolution will be evaluated elaborately during the NDA review.*

Discussion

The Division notified the Sponsor that detailed data will be needed for the NDA and that tighter disintegration testing data would be needed to substitute dissolution testing for routine batch release.

Question 5: Does FDA concur with the proposed ICH stability protocols for varenicline tartrate drug substance?

FDA Response:

- *Yes (See additional comments)*

Drug Substance Stability protocol

- *Degradants should be monitored.*
- *Forced degradation should be carried out using five conditions listed in ICH Q1A/B*
- *Statistical analysis of the 12-months stability data should be provided for all stability-indicating tests.*
- *Stability data should be provided in SAS transport format in conformance with electronic submission requirements.*

Discussion

The Division informed the Sponsor of []
[] the drug substance during stability studies and asked
the sponsor to monitor [] possible degradants []

Question 6: Does FDA concur with the proposed ICH stability protocols for varenicline tartrate drug product?

FDA Response:

- *Yes. See additional comments*

Drug Product Stability Protocol

- *Provide 12-months stability data and the statistical analysis of all stability-indicating test attributes.*
- *The reduced testing schedule should conform to ICH Q1A(R)/Q1D guidelines and the stability data should be analyzed pursuant to ICH Q1E.*
- *Justification for the proposed bracketing design should be provided.*
 - *The lower and upper extremes.*
 - *Worst-case scenario.*
- *Agency's Drug Product and Stability Guidances should be referenced (if final at the time of NDA).*

Discussion:

The stability protocol conforms to the expectations of ICH Q1F. The guidance states that for drug substances and products intended for registration applications within the ICH Tripartite regions, long term testing will typically be conducted at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$. It states further that the long term testing at $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$ can be a suitable alternative to $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\%$. In this case, for an application in the ICH Tripartite regions, no testing at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$ need be performed. Therefore, the Sponsor's choice of $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$ is acceptable.

Additional Issues on Manufacturing

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]

Discussion

The Division asked the sponsor to provide [] data and []
[] data from the primary NDA batches. The Division
also advised that the [] should include []
[]. This was noted to be
especially critical []
such as varenicline.

The Sponsor responded that they performed []
[] The Division advised the Sponsor that they expect
[] and that the sponsor may propose alternatives
with justification. The Division recommended [] testing
and pointed out that this should be done with validation batches as well as the
subsequent commercial batches. The Sponsor agreed to provide the data in support
of the [] []

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

/s/

Pratibha Rana
11/6/03 01:45:38 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-928	Efficacy Supplement Type SE-	Supplement Number
Drug: Varenicline 0.5 mg, 1 mg Tablets		Applicant: Pfizer Inc.
RPM: Dominic Chiapperino, Ph.D.		HFD-170 Phone # 301-796-1183
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
Chem class (NDAs only)		1
Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
		May 10, 2006
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 *CMC Pilot Program
User Fee Information		
User Fee		<input checked="" type="checkbox"/> Paid UF ID number PD3006237
User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		

Version: 6/16/2004

(Note: This can be determined by confirming whether the Division has received a written notice from the 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 box below (Exclusivity).

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the 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 applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

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 box below (Exclusivity).

If "Yes," a stay of approval must be requested. Determine if a 30-month stay is in effect, consult with the Director, Division of Operations, and the Office of Regulatory Policy (1-FD-007) and the Office of Legal Affairs (1-FD-008).

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	No
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(3), for the definition of "same drug" for an orphan drug (i.e., active moiety, strength, dosage form, and route of administration as that used for NDA chemical classification). 	() Yes. Application # _____ () No
Administrative Reviews (Project Manager: [redacted])	Being Review 4/13/06, Dominic [redacted], RPPM, DAARP

❖ Actions	
Proposed action	(X) AP () TA () AE () NA
Previous actions (specify type and date for each action taken)	
Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
Press Office notified of action (approval only)	(X) Yes () Not applicable
Indicate what types (if any) of information dissemination are anticipated	() None (X) Press Release () Talk Paper () Dear Health Care Professional Letter
Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
Most recent applicant-proposed labeling	
Original applicant-proposed labeling	X
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>) 	DDMAC review (5/12/06) DSRCS review (5/8/06) DMETS review (3/7/06 and 4/26/06)
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	X
Applicant proposed	X
Reviews	DMETS (4/26/06)
Post-marketing commitments	
Agency request for post-marketing commitments	X
Documentation of discussions and/or agreements relating to post-marketing commitments	X (see memo to file)
Outgoing correspondence (i.e., letters, E-mails, faxes)	X
Memoranda and Telecons	X
Minutes of Meetings	
EOP2 meeting (indicate date)	Clinical 1/27/03 CMC 11/6/03
Pre-NDA meeting (indicate date)	12/29/05
Pre-Approval Safety Conference (indicate date; approvals only)	4/6/06
Other	
Advisory Committee Meeting	
Date of Meeting	
48-hour alert	
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Office Director 5/10/06 Division Director 5/8/06 Medical Team Leader 5/9/06
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	Efficacy 5/9/06 Safety 5/9/06 SEALD 3/10/06
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
Safety Update review(s) (indicate date or location if incorporated in another review)	Safety clinical review above 5/9/06
Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	ODS 3/29/06
Pediatric Page(separate page for each indication addressing status of all age groups)	5/10/06
Demographic Worksheet (NME approvals only)	
❖ Statistical review(s) (indicate date for each review)	5/9/06
❖ Biopharmaceutical review(s) (indicate date for each review)	4/7/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	5/8/06
❖ Clinical Inspection Review Summary (DSI)	
Clinical studies	4/19/06
Bioequivalence studies	
CMC Information	
❖ CMC review(s) (indicate date for each review)	5/9/06 5/10/06
Environmental Assessment	
Categorical Exclusion (indicate review date)	5/9/06
Review & FONSI (indicate date of review)	
Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
Methods validation	() Completed (X) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	5/8/06 5/9/06
Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	3/17/06
❖ CAC/ECAC report	4/10/06

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) 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.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling