

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-928**

**Chemistry Review(s)**

CMC Team Leader Memo to file  
NDA 21-928: Chantix (varenicline) tablets  
Date: May 10, 2006  
Reviewer: Ravi S. Harapanhalli, Ph.D.

This memo serves to close the outstanding labeling comments included in the CMC review and to address two additional issues that were discussed with Pfizer on May 9-10, 2006, paving the way for approval recommendation from CMC perspective.

Overall recommendation: Approval

Review of Responses to Labeling comments:

The labeling comments were consolidated and short listed from DMETs comments and additional CMC comments were added. The list was e-mailed to Pfizer on 05/08/06 by the clinical PM, Dr. Dominic Chiapperino. Pfizer's responses to comments on container and closure labels were received on May 10, 2006 and are evaluated here.

A. General comments:

1. Increase the prominence of the established name and the dosage form name for better clarity and readability. Note that prominence is an overall effect of the font size, font style, font bolding, etc. and this should be at least half as prominent as is the tradename.

Response:

Pfizer agrees to increase the prominence of the established name by increasing the bolding. They also agree to increase the prominence of "TABLETS."

Evaluation: Adequate

2. Increase the prominence of all statements and wordings (e.g. NDC numbers, Rx only statement, strength, contents, storage statement, dosage and use, etc.) on the labels by better utilizing the available space.

Response:

Pfizer agreed to increase the prominence of the strength and the net contents statement. The size of NDC number, Rx only, and other standard language will also be increased in prominence.

Evaluation: Adequate

3. The appearance of bar across the letter "A" in Chantix is exaggerated, appears two-tone in color, and dissects the letter "H". Revise the bar across the letter "A"

to appear uniform with the rest of the proprietary name to improve readability by deleting the green arrow-type marking underneath the letters H and A in the tradename.

Response:

Pfizer agreed to revise the "A" in the CHANTIX logo on packaging to be the consistent font of the other letters in the proprietary name.

Evaluation: Adequate

4. When comparing the Chantix labels and labeling side-by-side, it was noted that the same color schemes are used for the different packaging configurations, i.e. a [ ] background with [ ] font and a [ ] background with [ ] font on certain Chantix labels. To avoid selection errors and confusion, revise the colors so they do not overlap in any way.

Response:

Pfizer agreed to revise packaging to remove [ ] color as described.

Evaluation: Adequate

5. The labels and labeling recommend using Chantix [ ]. Many patients may interpret [ ] to mean bedtime or close to bedtime. However, a potential adverse event is insomnia. Recommendations should be included as to the optimal time to take Chantix to prevent insomnia.

Response:

Pfizer agreed to not use the term [ ] to correspond with dosing on packaging.

Evaluation: Adequate

- B. Early experience kit (4-week starter kit and starter week)

Heat seal card-front:

6. There should be no intervening matter between the proprietary and established names and the product strength. The graphic design of the label [ ] separates the product name from the product strength. Relocate the strength to appear in conjunction with the proprietary and established names.

Response:

Pfizer agreed to revise the location of the product strength and relocate closer to the product name.

Evaluation: Adequate

6 Page(s) Withheld

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

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(4) Draft Labeling

**Overall recommendation:**

As discussed above, all issues pertaining to the labels and labeling, drug name and expression of strengths, and addition of a new package configuration have been resolved satisfactorily. The CMC review dated May 9, 2006 documents the basis for approval from CMC perspective. Together, the CMC review and this memo to file serve to justify the approval recommendation from CMC perspective.

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/s/

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Ravi Harapanhalli  
5/10/2006 05:17:03 PM  
CHEMIST



# **NDA 21-928**

## **Chantix (varenicline tartrate) Tablets**

### **Pfizer Pharmaceuticals**

**Stephen Miller, Ph.D. (Drug Substance)**

**Ying Wang, Ph.D. (Manufacturing Science)**

**Ravi Harapanhalli, Ph.D. (Drug Product and overall)**

### **ONDQA**

### **Pre-Marketing Assessment Divisions II & III**

### **CMC Review of Original NDA**

**For OND Division of Anesthesia, Analgesia, and  
Rheumatology Products (DAARP)**



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# Chemistry Review Data Sheet

1. NDA 21-928

2. Review #1

3. REVIEW DATE: April 24, 2006

4. REVIEWERS:

Ying Wang (Manufacturing Science Aspects)

Steve Miller (Drug Substance Aspects)

Ravi Harapanhalli (Drug Product Aspects)

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
CMC EOP-2 Meeting	October 9, 2003
CMC Development Meeting	October 14, 2004
PQAS Discussion	April 19, 2005
CMC Pilot Program Discussions	August 11, 2005; Oct 28, 2005
Pharmaceutical Development Overview	November 5, 2005

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Stamp Date</u>
Original NDA Submission	Nov 09, 2005
BC-Stability Update	Feb 7, 2006
Labeling amendment BL	March 14, 2006
Response to CDER CMC Letter #1	Mar 20, 2006 (letter date)
Response to CDER CMC Letter #2	Mar 27, 2006 (letter date)
BC	Apr 10, 2006
BL-Revised Package Labeling; New Trademark	Apr 11, 2006
Responses to CDER CMC Letter # 3	April 28, 2006 (letter date)
Response to CDER CMC Letter # 4 (05/02/06)	May 5, 2006

Note: The CMC amendments may not be in the EDR, but were submitted to ONDQA CMC Pilot program.

7. NAME & ADDRESS OF APPLICANT:

Y. Wang/S. Miller/R. Harapanhalli

Pharmaceutical Quality Assessment

4



Chemistry Assessment Section

Name: Pfizer Inc.

Address: 50 Pequot Ave.; New London, CT 06320

Representative: Michael J. Page, B.Sc.

Telephone: (860)715-1110

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Chantix Tablets
- b) Non-Proprietary Name (USAN): Varenicline Tartrate
- c) Code Name/# (ONDC only): CP 526,555
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: NDA is submitted under 505(b)(1)

10. PHARMACOL. CATEGORY: Smoking Cessation

11. DOSAGE FORM: Tablet - Immediate Release

12. STRENGTH/POTENCY: 0.5 mg and 1.0 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

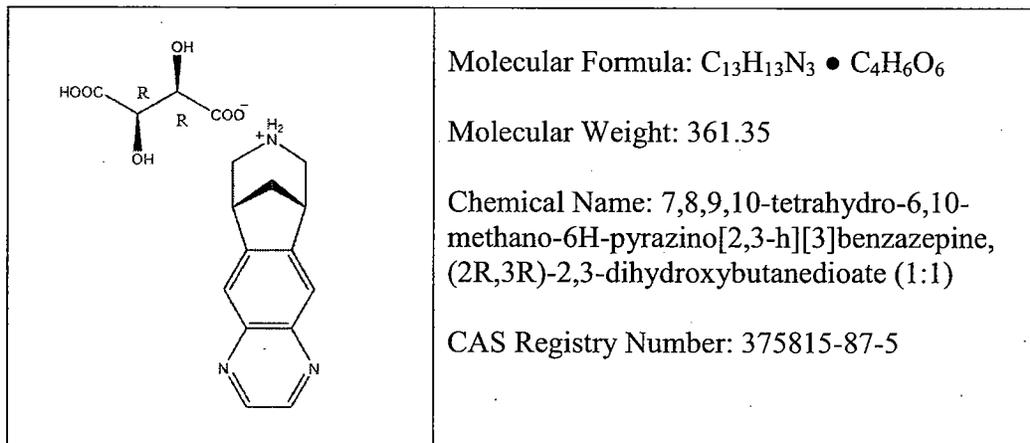
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

## Chemistry Assessment Section

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



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
[ ]	III	[ ]	[ ]	3	Adequate	March 9, 2006 (Chong Ho Kim)	Acceptable

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

## B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND 58,994		Varenicline Immediate Release Tabs



## Chemistry Assessment Section

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J

## 18. STATUS:

**ONDQA related consults:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA (Did not consult) since updated real time stability data showed no significant change in any of the quality attributes.	February 7, 2006	R. S. Harapanhalli
EES	Overall Acceptable	Apr 7, 2006	Albinus M. D Sa, Consumer Safety Officer, Office of Compliance
Pharm/Tox	Genotoxic Impurities Adequately Controlled		S. Miller (see also Pharm/Tox review)
Biopharm	Discussed and agreed that disintegration may be used in lieu of dissolution testing of the final drug product since the former is shown to be more sensitive than the latter. 3 BE studies described in the P.2 section were deemed adequate to support the bridging of formulation changes made during Phases 2 and 3.	April 3, 2006	R. S. Harapanhalli and Srikant Nallani
LNC	NA. Appropriate USAN name and common dosage form		R. S. Harapanhalli
Methods Validation	None Necessary. The procedures do not qualify for any of the seven criteria to initiate method validation studies.		R. S. Harapanhalli
ODS/DMETS	Trademark Revised from Champix to Chantix and comments on container and cartons were provided	May 5, 2006	Alina Mahmud, TL, DMETS
EA	Exemption Adequately Justified		R. S. Harapanhalli
Microbiology	NA. Data supporting that the solid oral dosage form does not promote microbial growth.		R. S. Harapanhalli

Chemistry Assessment Section

# The Chemistry Review for NDA 21-928

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

L

J. Pfizer's responses dated April 28, 2006 to the Agency deficiency letter dated April 20, 2006 were deemed adequate and all critical CMC issues pertaining to approvability were resolved satisfactorily. An acceptable cGMP recommendation was made by the Office of Compliance on April 7, 2006. L

J. The NDA is recommended for approval from the CMC perspective. The following statement should be included regarding the product shelf life.

"A shelf life of 24 months proposed for this drug product. L

and stored at room temperature, 15 to 30 °C (59–86 °F) is granted." J

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

L

## Chemistry Assessment Section

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)**

Varenicline is [ ] made by conventional chemical synthesis. The tartrate salt was selected to be the drug substance based on favorable chemical and biophysical properties. Varenicline tartrate is [ ] highly soluble, white to off-white to slightly yellow solid with a molecular weight of 361.35 and a melting point of between [ ] [ ] The very high solubility of varenicline tartrate in water at physiologically relevant pH values means that there is very low risk that physical parameters [ ] [ ] will adversely affect dissolution of the tablet or absorption from the gut. [ ] [ ] varenicline tartrate have been identified and characterized [ ] [ ] during development - [ ]

drug substance is considered highly soluble in all pH ranges. Additionally, the drug substance [ ] [ ] Therefore, [ ]

[ ] Based on the results of excretion pattern of total radioactivity after oral administration of [<sup>14</sup>C] varenicline to healthy human subjects wherein the vast majority of recovered radioactivity was excreted in the urine, and the permeability of [<sup>14</sup>C] varenicline through the Caco-2 cell model, the drug is shown to possess high permeability. Taken together, the solubility and permeability data and rapid dissolution profiles in a wide range of media supported BCS Class 1 for this drug.

Chantix (varenicline tartrate) is indicated for smoking cessation. Chantix is available in 0.5-mg and 1.0-mg dose strengths - as white to off-white, film-coated, capsular biconvex tablets debossed with "Pfizer" on one side and "CHX 0.5" on the other side for the 0.5 mg strength and as light blue, film-coated capsular biconvex tablets debossed with "Pfizer" on one side and "CHX 1.0" on the other side for the 1.0 mg strength. The drug product is [ ]

[ ] The drug product is an immediate-release formulation [ ]

[ ] Pharmaceutical excipients used are conventional in nature and consist of microcrystalline cellulose, dibasic calcium phosphate, anhydrous, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White [ ] [ ], and Opadry® Clear [ ] [ ]

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

The drug product is indicated for smoking cessation and patient should decide on a *quit date* when he/she will stop smoking and then start using CHANTIX 7 to 14 days before the quit date. This lets CHANTIX build up in patient's body system and he/she can keep smoking during this time. It is best to STOP SMOKING completely between Day 8 and





Chemistry Assessment Section

The quality attribute of the drug substance that is most directly linked to safety is the level of [ ] impurities in the DS. Several of these impurities, [ ] have structures that are considered to have genotoxicity alerts. Based on the EMEA CHMP draft guidance on genotoxic impurities, Pfizer proposes to limit these impurities to [ ] ppm, which gives a daily exposure of [ ] ug/day at a dosing level of 2 mg varenicline tartrate per day. In consultation with the pharmacology/toxicology discipline, a limit of [ ] ppm limit was applied to the total of the impurities with genotoxicity concerns and Pfizer agreed to this during the March 1, 2006 meeting. This is based on the expectation that these compounds have similar mechanisms of genotoxicity, so the limit should apply to the total. Since control of these genotoxic impurities can only be achieved by [ ] [ ]

[ ] in an IR letter dated April 21, 2006, Pfizer was asked to provide revisions to the NDA to include the following:

- a) [ ]
- b)
- c)

Also, Pfizer was asked to designate [ ] a starting material rather than raw material and to provide a brief justification for its proposed specifications. Pfizer's responses dated April 28, 2006 addressed all these issues satisfactorily.

Because the drug is formulated at very low dose [ ] and because the drug product is made by [ ] the drug substance [ ]

[ ] This is adequately controlled through [ ] of the DS, [ ] for each batch of DS, and in conjunction with additional controls of DP manufacturing parameters. Therefore, the proposed acceptance criteria for the [ ] was considered acceptable wherein [ ] [ ] was proposed in addition to [ ] was not deemed necessary.

Varenicline tartrate has very good stability profile and there were no significant changes in the accelerated testing conditions. The degradation pathways were identified and statistical analyses of all stability-indicating parameters were provided to support a [ ] retest interval. Therefore, with the [ ] of stability data supplied in the amendment of Feb 7, 2006, a [ ] retest interval was granted when stored at room temperature, or below 30 deg C. Appropriate commitments to post-approval stability studies, under both long-term (30deg C/65% RH) and accelerated conditions, were also provided.

Drug product:

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

       § 552(b)(5) Deliberative Process

       § 552(b)(4) Draft Labeling

## Chemistry Assessment Section

[

]

Therefore, in a letter dated April 21, 2006, they were asked to provide the following clarification in the dosage form monographs (DFM) of the drug product.

- a) A description of [ ] testing using [ ] for test [ ]
- b) A description of [ ] using [ ] for both validation and routine commercial batches.

Pfizer's responses dated April 28, 2006 addressed these issues satisfactorily. The DFM was revised to include a statement [ ] and adequate data from [ ] validation batches, [ ] additional commercial batches from [ ] drug substance and [ ] commercial-scale batches was provided to support test [ ]

The drug product specifications were based on ICH Q3B (R) and ICH Q6A and consisted of [ ]

Detailed descriptions of analytical methods were provided and method validation data was generated in accordance with ICH guidelines and included specificity, linearity, precision, limits of quantification, accuracy and robustness as appropriate. Method validation/verification will not be requested at the FDA Laboratories. Although dissolution testing is not included in the specifications, it is acceptable based on the ICH Q6A and Agency criteria that for a BCS Class 1 drug if disintegration is shown to correlate with dissolution and is at least as sensitive as is the dissolution in identifying formulation discrepancies, then disintegration could replace dissolution. The data indicated that disintegration was in fact more sensitive than was dissolution. Additionally, the firm has committed to evaluating both dissolution and disintegration for primary and site specific stability programs.

Batch analyses summaries of six 0.5 mg and six 1.0 mg batches manufactured by the commercial manufacturing process at Pfizer Freiburg (primary stability batches) and Illertissen Germany (commercial site qualification batches) were provided. Assays ranged from [ ] the [ ] for [ ] testing ranged [ ] the disintegration times were less than one minute, the [ ] ranged [ ] the individual and the total degradation products were not more than [ ]

## Chemistry Assessment Section

The stability studies were conducted in accordance with ICH guideline Q1A (R2). The primary program consisted of three batches of each strength (0.5 and 1.0 mg tablets) manufactured at the Pfizer facility in Freiburg, Germany. In addition, supportive and site specific stability programs consisting of one batch of each strength were initiated at the commercial manufacturing site in Illertissen, Germany. The site-specific program batches were manufactured using commercial components and composition at the commercial scale. Updated stability data submitted on February 7, 2006 included 12 months primary stability data for three batches of each strength, 6 months of site-specific stability data for one batch of each strength made at the intended commercial site, and [ ] of supportive stability data. There were no or insignificant changes in the assay, [ ] therefore the data did not warrant further statistical analysis. For example, individual and total degradation products did not exceed [ ] limit of quantitation. Also, there were no or insignificant changes at the accelerated conditions, little or no changes during [ ] for the supportive batches, and no significant changes in the samples under stress conditions of 25°C/85 % RH and 50°C/20% RH for 3 months. Therefore, a shelf life of 24 months proposed for this drug product [ ] stored at room temperature, 15 to 30 °C (59–86 °F) is well justified and is granted.

An overall compliance recommendation was made on April 7, 2006 with an acceptable cGMP status for all facilities involved in the manufacture, packaging, and testing of the drug substance and the drug product.

Thus, the NDA is recommended for approval from CMC perspective.

### III. Administrative

#### A. Reviewer's Signature

*{See appended electronic signature page}*

Steve Miller, Pharmaceutical Assessment Lead, ONDQA  
Ying Wang, Reviewer, ONDQA  
Ravi S. Harapanhalli, Branch Chief, ONDQA

#### B. Endorsement Block

CMC Reviewers' Names/Date: Ying Wang, Ph.D., Stephen Miller, Ph.D., and Ravi S. Harapanhalli, Ph.D., May 9, 2006  
ONDQA Deputy Director's Name/Date: Chi-wan Chen, Ph.D., May 9, 2006  
PM's Name/Date: Amy Bertha, ONDQA PM, Dominic Chiapperino, DAARP/OND PM

#### C. CC Block

Celia Winchell, Medical TL, DAARP, Howard Josefberg, Medical Officer, DAARP



## CHEMISTRY REVIEW OF NDA 21-928



Chemistry Assessment Section

Dan Mellon, Pharm/Tox TL, Mamta De, Pharm/Tox reviewer, DAARP

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