# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-030**

# CHEMISTRY REVIEW(S)

**MEMORANDUM**

Date: September 23, 2008

To: NDA 22-030

From: Elaine Morefield, Ph.D.
Division Director
Pre-marketing Assessment Division II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-030 Toviaz® (fesoteridine fumarate) Extended Release Tablets, by Pfizer, Inc.

NDA 22-030 is for Toviaz® (fesoteridine fumarate) extended release tablets for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and labels have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for approval.

I have assessed the ONDQA review of NDA 22-030. I believe that there are adequate manufacturing procedures and controls for production of a quality product. I concur with the approval recommendation from a CMC perspective.

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

/s/

Elaine Morefield
10/16/2008 04:18:18 PM
CHEMIST

# NDA 22-030

## TOVIAZ
**(Fesoterodine fumarate)**
**{Trade name is not finalized}**

**Extended release tablets**

**Pfizer, Inc.**

Division of Reproductive and Urologic Products

**Rajiv Agarwal**

DIVISION OF PRE-MARKETING DRUG QUALITY ASSESSMENT
(Branch III, Division II)

# Chemistry Review Data Sheet

1. NDA # 22-030
2. REVIEW #: 2
3. REVIEW DATE: 10-AUG-2008
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS:

| | |
|---|---|
| Original | 17-MAR-2006 |
| Amendment | 15-MAY-2006 |
| Amendment | 03-AUG-2006 |
| Amendment | 06-OCT-2006 |
| Amendment | 16-NOV-2006 |
| Amendment | 22-NOV-2006 |
| Amendment | 11-JAN-2007 |
| CMC review # 1 | 19-JAN-2007 |
| Approvable letter | 25-JAN-2007 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Complete Response | 01-MAY-2008 |
| Amendment | 19-MAY-2008 |
| Amendment | 18-JUN-2008 |

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer, Inc.

Address: 235 East 42nd Street, New York, NY 10017

Representative: Alan McEmber, Director, Worldwide Regulatory

Telephone: 212-733-0081

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: TOVIAZ
b) Non-Proprietary Name (USAN): fesoterodine fumarate
c) Code Name/# (ONDQA only): SPM 907
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: For the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency

11. DOSAGE FORM: Tablet (Extended release)

12. STRENGTH/POTENCY: 4 and 8 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

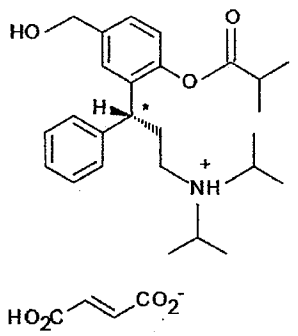
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

____x__Not a SPOTS product

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

**Chemical Name:**

**Isobutyric acid-2-[R-3-diisopropylammonium-1-phenylpropyl]-4-hydroxymethyl)phenyl ester hydrogen fumarate**




**Molecular Formula**: $C_{30}H_{41}NO_7$

**Molecular weight**: 527.66 (salt), 411.59 (base)

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | III | | | 3 | Adequate | 16-JUL-2004 | Li-Shan Hsieh, NDA 21-743 |
| | III | | | 3 | Adequate | 17-MAR-2003 | Young-de Lu, NDA 21-545 |
| | III | | | 3 | Adequate | 02-SEP-2003 | Edwin Jao, NDA 21-621 |
| | III | | | 3 | Adequate | 11-MAR-2005 | Gene W. Holbert, NDA 21-266 |
| | III | | | 3 | Adequate | 20-OCT-2003 | Ramesh Sood, NDA 20-334 |

b(4)

[1] 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")

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

**B. Other Documents:**

- IND 51,232
- CMC review # 1: 19-JAN-2007

18. STATUS:

**ONDQA:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | Acceptable | 15-JUL-2008 | Office of Compliance |
| Methods Validation | N/A | | |
| DMEPA | Pending | | |
| EA | Categorical exclusion Granted | 19-JAN-2007 | Dr. Rajiv Agarwal |

# The Chemistry Review for NDA 22-030

**The Executive Summary**

*I. Recommendations*

*A. Recommendation and Conclusion on Approvability*

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and labels have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for "Approval".

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

None

*II. Summary of Chemistry Assessments*

*A. Description of the Drug Product(s) and Drug Substance(s)*

**Drug product:**

TOVIAZ (fesoterodine fumarate), 4 mg and 8 mg, is an extended release tablet, which is either light blue (4 mg) or blue (8 mg) in color, oval in shape, and film coated. Fesoterodine is immediately de-esterified to its active metabolite (a diol), R-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol (SPM 7605).

This product is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The tablets are manufactured by **Schwarz Pharma Manufacturing Inc.**, in **Germany** and tested, packaged and labeled by **Schwarz Pharma, IN, USA.** The final recommendation from the Office of Compliance for the drug product manufacturing and testing sites is acceptable.

The extended release tablet system of fesoterodine tablet is a

b(4)

The quality of the tablets is controlled by the following tests:

All the respective acceptance criteria are deemed satisfactory except for the acceptance criteria for impurities.

b(4)

As per ICH Q6A, decision tree # 2, Division recommended and applicant accepted that the acceptance criteria of the specified impurities

*(For details regarding this section, refer to CMC review # 1 dated 19-JAN-2007).*

Fesoterodine fumarate extended release tablets were developed with engraved on one side of the tablets. In the Complete Response, the engraving has been modified for the commercial formulation to take into account the change in product ownership. For lower strength tablets (4 mg), "FS" will be engraved on one side and "FT" will be engraved on one side of the 8 mg strength tablets.

To support the change in engraving, comparative dissolution testing was performed in the specified release media (Phosphate buffer pH 6.8) between the proposed commercial formulations with "FS" or "FT" engraving (4 mg and 8 mg strengths, respectively) and the current formulations with engraving (4 mg and 8 mg strengths). The data showed that tablets engraved with "FS" (4 mg strength tablets) or "FT" (8 mg strength tablets) show equivalent dissolution to those engraved with . The change in engraving is acceptable. b(4)

Throughout clinical development, five sustained release formulations were used. The basic composition of all tablet formulations and the basic manufacturing process remained the same.

b(4)

The to-be-marketed tablets for each strength will be manufactured by the process using uses the formulation "F" which was used in the phase 3 clinical trails. b(4)

Subsequent to the change of product ownership to Pfizer, additional packaging presentations cc bottles) have been identified in the current submission. The applicant added 5 new DMFs from different suppliers related to the cap and bottles. The information pertaining to their use in packaging of a solid oral dosage form is reviewed previously and was found adequate.

The tablets are packaged in two different packaging configurations (bottles and blisters). Bottles, re made of and contain 30 and 90 tablets, respectively. The is used for all bottle sizes. Bottles are secured with cap Depending on the size of the bottle, For physician's samples, the blister contains 14 tablets per card Although the applicant did not state that the physician samples are child resistant, it appears that the packaging in tear/push blister will make the blisters packages child resistant (16 CFR 1700). Stability data (drug product) supports their usage in the drug product. The presented packaging configuration also meet the USP <661> compatibility and suitability requirements. b(4)

Based on the real time data, the applicant is requesting a 24 months of shelf life. During the first review cycle, based on the stability studies on primary batches, it is determined that a 24 months of expiration date may be granted for the product packaged in bottles and blisters. Based on the stability characteristics of the drug product, the applicant proposed and FDA accepted the storage condition to be "Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture".

A final decision on the trade name "TOVIAZ" has not been made by DMEPA.

**Drug Substance:**

Fesoterodine fumarate is a new molecular entity and is manufactured by Schwarz & Company in Shannon, Ireland. Fesoterodine fumarate is the dextrorotary enantiomer of a derivative of 3,3-diphenylpropylamine and is a diol, which is an active metabolite. The structure of drug substance includes one chiral center and its melts at Both salt and base are freely soluble in various

b(4)

buffers. The salt is freely soluble [redacted] in water [redacted] mg/ml). At a temperature of [redacted] the pKa-value of this drug substance is [redacted]

The quality of the drug substance is controlled by specification set by the manufacturer, which includes, [redacted] They are deemed satisfactory.

b(4)

Drug substance, when stored at accelerated conditions / [redacted]

b(4)

The final recommendation from the Office of Compliance for **Schwarz, Shannon, Ireland site** is **ACCEPTABLE (Attachment-1)**.

The applicant is requesting a [redacted] of re-test period. Granted.

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

TOVIAZ (fesoterodine fumarate) is an extended-release tablet for once-daily oral administration.

***C. Basis for Approvability or Not-Approval Recommendation***

This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the shelf life. The Office of Compliance has issued an "Acceptable" overall recommendation (**Attachment-1**) for all the facilities involved on 15-JUL-2008. Labels have required information.

The DMEPA has not made a final decision on the proposed trade name. The absence of an approved trade name is not an approvability issue [21 CFR 201.57 (a) (2)].

***III. Administrative***

***A. Reviewer's Signature: Captured electronically in DFS***

***B. Endorsement Block:*** RAgarwal/ MRhee

***C. CC Block:*** EMorefield/DFChristner/CHayes

# 23 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Chemistry-* 1

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

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/s/

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Elaine Morefield
1/22/2007 06:43:27 PM
CHEMIST

# NDA 22-030

[redacted] b(4)

**(Fesoterodine fumarate)**

**Extended release tablets**

**Schwarz Biosciences, Inc.**

Division of Reproductive and Urologic Products

**Rajiv Agarwal**

DIVISION OF PRE-MARKETING DRUG QUALITY ASSESSMENT
(Branch III, Division II)

# Chemistry Review Data Sheet

1. NDA # 22-030
2. REVIEW #: 1
3. REVIEW DATE: 18-JAN-2006
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 17-MAR-2006 |
| Amendment | 15-MAY-2006 |
| Amendment | 03-AUG-2006 |
| Amendment | 06-OCT-2006 |
| Amendment | 16-NOV-2006 |
| Amendment | 22-NOV-2006 |
| Amendment | 11-JAN-2007 |

7. NAME & ADDRESS OF APPLICANT:

Name: Schwarz Biosciences, Inc.

Address: 8010 Arco Corporate Drive, Suite 100, Raleigh, NC 27617

Representative: Alan Blumberg, Sr. Director, Regulatory Affairs

Telephone: 919-767-2513

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: [redacted]
b) Non-Proprietary Name (USAN): fesoterodine fumarate
c) Code Name/# (ONDQA only): SPM 907
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: For the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency

11. DOSAGE FORM: Tablet (Extended release)

12. STRENGTH/POTENCY: 4 and 8 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

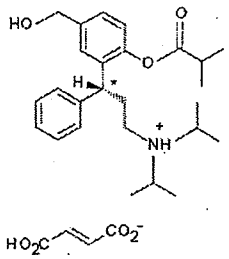
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

____x__Not a SPOTS product

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

**Chemical Name:**

**Isobutyric acid-2-[R-3-diisopropylammonium-1-phenylpropyl]-4-hydroxymethyl)phenyl ester hydrogen fumarate**



**Molecular Formula:** $C_{30}H_{41}NO_7$

**Molecular weight:** 527.66 (salt), 411.59 (base)

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| [redacted] | III | [redacted] | [redacted] | 4 | N/A | | Sufficient information in the NDA |
| | III | | | 3 | Adequate | 26-JUL-2004 | Dr. L-S Hsieh for NDA 21-743 |
| | III | | | 3 | Adequate | 26-JUL-2004 | Dr. L-S Hsieh for NDA 21-743 |

b(4)

| | | | | | |
|---|---|---|---|---|---|
| III | 3 | Adequate | 20-AUG-2001 | Dr. R. Uppoor for NDA 21-290 | |
| III | 3 | Adequate | 12-JAN-2005 | Dr. R. Manurawe for NDA [redacted] | |
| III | 3 | Adequate | 27-JUL-2004 | Dr. S. Pope for NDA 21-663 | |
| III | 3 | Adequate | 04-NOV-2005 | Dr. C-H Niu for NDA [redacted] | b(4) |
| III | 3 | Adequate | 25-AUG-2004 | Dr. A. Schroeder for NDA 21-585 | |
| III | 4 | N/A | | Sufficient information in the NDA | |
| III | 3 | Adequate | 15-JUN-2000 | Dr. K. Swiss for NDA 21-165 | |
| III | 4 | N/A | | Sufficient information in the NDA | |

[1] 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")

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

**B. Other Documents:**

- IND 51,232
- EOP2 meeting 13-JUL-04
- Pre NDA (CMC) 18-NOV-05
- 74-day letter dated 9-JUN-2006
- CMC IR letter: 13-DEC-2006
- CMC labeling IR: 17-JAN-2007

18. STATUS:

**ONDQA:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | **Withhold** | 9-NOV-2006 | Office of Compliance |
| Methods Validation | The method validation package will be sent to and validated by FDA laboratories. | | |
| DMETS | Acceptable | 11-JAN-2007 | Ms. Laura Pincock |
| EA | Categorical exclusion Granted | 5-DEC-2006 | Dr. Rajiv Agarwal |

# The Chemistry Review for NDA 22-030

**The Executive Summary**

*I. Recommendations*

*A. Recommendation and Conclusion on Approvability*

This application is **approvable** from Chemistry, Manufacturing and Control standpoint based on the **WITHHOLD** recommendation from the Office of Compliance for the Drug substance manufacturing site in Ireland, and some labeling issues.

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

None

*II. Summary of Chemistry Assessments*

*A. Description of the Drug Product(s) and Drug Substance(s)*

**Drug product:**

[redacted] (fesoterodine fumarate), 4 mg and 8 mg, is an extended release tablet, which is either light blue (4 mg) or blue (8 mg) in color, oval in shape, film coated and engraved on one side with SP. Fesoterodine is immediately de-esterified to its active metabolite (a diol), R-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol (SPM 7605), which is a muscarinic receptor antagonist. b(4)

This product is indicated for the treatment of overactive bladder. The tablets are manufactured by **Schwarz Pharma Manufacturing Inc., in Germany** and tested, packaged and labeled by **Schwarz Pharma, IN, USA.** The final recommendation from the Office of Compliance for the drug product manufacturing and testing sites is acceptable.

The extended release tablet system of fesoterodine tablet is a [redacted] b(4)

The quality of the tablets is controlled by tests: [redacted] All the respective acceptance criteria are deemed satisfactory except for the acceptance criteria of impurities. [redacted] As per ICH Q6A, decision tree # 2, Division recommended that the acceptance criteria of the specified impurities be [redacted]

The applicant did not establish acceptance criteria for chiral purity in drug product but because [redacted] of the drug substance under the recommended storage conditions, it is acceptable. The drug product is recommended to be stored at [redacted] b(4)

b(4)

Throughout clinical development, five sustained release formulations were used. The basic composition of all tablet formulations and the basic manufacturing process remained the same.

b(4)

The to-be-marketed tablets for each strength will be manufactured by uses the formulation "F" which was used in the phase 3 clinical trails.

b(4)

The tablets are packaged in two different packaging configurations (bottles and blisters). Bottles, are made of contain, 30 and 90 tablets, respectively. Whereas the blister contain 14 tablets per blister card (for physicians samples). Bottles are secured with cap The bottles will Stability data (drug product) supports their usage in the drug product. The presented packaging configuration also meet the USP <661> compatibility and suitability requirements. The aluminum/aluminum blisters are for physicians sample only.

Sponsor is requesting a 24 months of shelf life. Based on the stability studies on primary batches, 24 months of expiry date may be granted for the product packaged in bottles and blisters. Based on the stability characteristics of the drug product, the applicant proposed and FDA accepted the storage condition to be "Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture".

The trade name is Acceptable to DMETS. b(4)

**Drug Substance:**

Fesoterodine is a new molecular entity and is manufactured by Schwarz and Company in Shannon, Ireland. Fesoterodine fumarate is the dextrorotary enantiomer of a derivative of 3,3-diphenylpropylamine and is / a diol, which is an active metabolite. The structure of drug substance includes one chiral center and its melts at Both salt and base are freely soluble in various buffers. The salt is freely soluble in water At a temperature o he pKa-value of this drug substance is

b(4)

The quality of the drug substance is controlled by specification set by the manufacturer, which includes, They are deemed satisfactory.

Drug substance, when stored at accelerated conditions

The final recommendation from the Office of Compliance for **Schwarz, Ireland site is withhold** (*see Attached 1*) because the site is not ready for inspection. In a submission dated 15-MAY-2006, the applicant stated the manufacturing site will not be ready for PAI inspection and will likely extend beyond the PAI readiness date of July, 2007 as specified in their NDA submission.

The applicant is requesting a [redacted] of re-test period. Granted.

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

[redacted] (fesoterodine fumarate) is an extended-release tablet for once-daily oral administration. b(4)

***C. Basis for Approvability or Not-Approval Recommendation***

This application is **approvable** from Chemistry, Manufacturing and Control standpoint based on the **WITHHOLD** recommendation from the Office of Compliance for the Drug substance manufacturing site in Ireland, and the following labeling issues which were conveyed to the applicant on 17-JAN-2007.

- The "X" graphic which precedes the proprietary name should be removed on all labels.
- Replace the word "Trade Name" with [redacted] in the PI and PPI.
- In the "How Supplied" section, the NDC #s for the 4 mg and 8 mg blister presentations in the PI do not match the NDC #s provided on the blister labels. Please correct the NDC #s so that they are the same on both the blister labels and the PI. b(4)
- [redacted]

*III. Administrative*

***A. Reviewer's Signature: Captured electronically in DFS***

***B. Endorsement Block:*** RAgarwal/ MRhee

***C. CC Block:*** EMorefield/Jean Makie/DFChristner

53 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Chemistry* 2

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

/s/
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Rajiv Agarwal
1/19/2007 09:02:37 AM
CHEMIST

Moo-Jhong Rhee
1/19/2007 11:45:43 AM
CHEMIST
Chief, Branch III

# Initial Quality Assessment
# Branch III
# Pre-Marketing Assessment Division II

| | |
|---|---|
| **OND Division:** | Division of Reproductive and Urologic Products |
| **NDA:** | 22-030 |
| **Applicant:** | Schwarz Biosciences, Inc. |
| **Stamp Date:** | 27-Mar-2006 (04-Apr-2006 posted on EDR) |
| **PDUFA Date:** | 26-Jan-2007 |
| **Trademark:** | None proposed |
| **Established Name:** | Fesoterodine fumarate |
| **Dosage Form:** | Extended-release tablet |
| **Route of Administration:** | Oral |
| **Indication:** | Overactive Bladder |
| **PAL:** | Donna F. Christner, Ph.D. |

| | YES | NO |
|---|---|---|
| **ONDQA Fileability:** | x | |
| **Comments for 74-Day Letter** | x | |

**Summary and Critical Issues:**

**A. Summary**

The drug product is an extended-release tablet. The sponsor refers to it as sustained release throughout the package, but is aware that the correct terminology for the US market is extended-release and the packaging is labeled to reflect this. The tablets are blue film-coated tablets with an engravure on one side. The 4 mg tablet is light blue, while the 8 mg tablet is blue. Tablets are packaged in HDPE bottles (30 or 90 tablets) for the commercial presentation and in Al-Al blisters for the physicians sample.

Fesoterodine fumarate is a new molecular entity which is a white to off-white powder, freely soluble in aqueous solvents, soluble in polar organic solvents and practically insoluble in heptane. It is the single (R)-enantiomer. The drug substance [redacted] the diol SPM 7605, which is the major metabolite. Labeling states that upon use, fesoterodine is immediately de-esterified to its active metabolite. b(4)

Clinical studies for this NDA have been performed under IND 51,232. The following CMC related meetings/correspondences are captured in DFS:

- Comments were sent to the sponsor after the 30-day safety review.
- An EOP2 meeting was held on 13-Jul-2004.
- A CMC preNDA meeting was held on 18-Nov-2005.
- A reply to a General Correspondence dated 12-Jan-2006 was generated.

An overview of the application is provided in the ASSESSMENT NOTES at the end of this document. DMFs are provided for non-compendial excipients and container closure systems. Relevant reviews are outline in the DMF table.

## B. Critical issues for review

The sponsor has identified a number of steps in the synthetic pathway that are critical to the quality of the drug substance. Controls will need to be analyzed to determine if they are adequate to assure drug substance quality.

Because the drug substance [redacted] assurance should be provided that the drug substance is adequately protected during shipping. b(4)

The new synthesis impurity [redacted] has been measured at levels up to [redacted], which is [redacted] the level for qualification (0.15%) as per ICH Q3A. The sponsor has used these batches in Phase 1-3 trials, but has not performed toxicology studies using these batches. The sponsor states that the impurity is qualified because levels are [redacted] the ICH qualification guidelines. b(4)

Other review issues are provided below in the Comments for the 74-day Letter.

## C. Comments for 74-Day Letter

*Please comment on what controls are in place to assure that the drug substance is stored at the correct temperature range during shipping, and whether the drug substance is tested at the drug product manufacturing facility prior to use to assure that degradation due to moisture and temperature sensitivity has not occurred.*

*Please confirm that the engravure for your tablets is [redacted] as stated in the General Correspondence dated 12-Jan-2006. If this is not correct, provide the correct information. Please comment on whether the clinical trial supplies had the same engravure.* b(4)

*An additional time point should be added to the dissolution specifications between the 4 hour and 16 hour draws. We recommend a draw at either 8 or 10 hours. Please submit a proposal.*

*Please be aware that if a decision is made to package drug product in blisters for commercial distribution, the blister packs would need to comply with 16 CFR 1700.14(a)(10) for child resistance.*

*Please submit additional stability data as soon as it becomes available in order to determine expiry.*

*Please submit a tradename to allow complete review of the labeling.*

## D. Recommendation:

This NDA was fileable from a CMC perspective on 11-May-2006. Preliminary comments were included for the 74-day letter. A single reviewer, Rajiv Agarwal, has been assigned and will evaluate the application to request any additional information deemed necessary.

On 15-May-2006, the sponsor informed the Division via email that the drug substance manufacturing site would not be available for inspection until after the PAI readiness date of September 2006. The sponsor states that [redacted] b(4) It was not known if the changes would affect the scale of the drug substance manufacturing process and if the synthetic pathway and the resulting impurities would be the same as those submitted originally in the NDA. Because a site should be ready for inspection upon submission of the NDA, and because there is no data to indicate what the changes are, this change of events was brought to the attention of Dr. Elaine Morefield, ONDQA, DPMA II Division Director, and Dr. Moo-Jhong Rhee, ONDQA, DPMA II Branch III Branch Chief. Dr. Morefield and Dr. Rhee determined that this may be a refuse-to-file decision for CMC.

A tcon was held on 16-May-2006 with the sponsor. The sponsor stated during the tcon that the change in the manufacturing site [redacted] b(4) This [redacted] would make the site not ready for inspection until late December 2006, and the sponsor suggested the inspection be scheduled in January 2007 (the PDUFA date is 27-Jan-2006). On 17-May-2006, the sponsor sent a General Correspondence outlining the changes, stating the site changes would be finished during the fourth quarter of 2006, and that the site could be inspected sometime within that time period. This information was sent to the Office of Compliance (see ASSESSMENT NOTES for email string). Office of Compliance stated that the EES would still be pending if no inspection could be held. With this information, Dr. Rhee recommended a RTF decision.

On 23-May-2006, John Dietrick, DFI Team Leader, stated that a withhold recommendation could be made if the site was not ready for inspection (see second email string), allowing the Division to take an action on the PDUFA date. Therefore, **this NDA can be filed from an ONDQA perspective.**

Although the timeline for the review will be decided upon at the Filing meeting, under the GRMP guidances, which are being closely adhered to by the clinical division, the review will need to be completed by November 2006. The PDUFA date is 27-Jan-2007.

Donna F. Christner, Ph.D.

# 21 Page(s) Withheld

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_____ Draft Labeling (b4)

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/s/
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Donna Christner
5/24/2006 11:35:07 AM
CHEMIST

Moo-Jhong Rhee
5/24/2006 12:00:30 PM
CHEMIST
Chief, Branch III