CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202514Orig1s000

CHEMISTRY REVIEW(S)

NDA 202-514

ZIOPTAN™ (tafluprost ophthalmic solution) 0.0015%

Merck Sharp & Dohme Co

Maotang Zhou, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V

CMC REVIEW OF NDA 202-514
For the Division of Transplant and Ophthalmology Products

CMC Review Data Sheet

1. NDA 202-514

2. REVIEW #: 3

3. REVIEW DATE: 30-Jan-2012

4. REVIEWER: Maotang Zhou, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 62,690 submission	23-May-2001
Original IND 62,690 CMC review	23-July-2001
End-of-phase-2 meeting (No CMC issues discussed)	24-Aug-2009
Pre-NDA meeting	13-Aug-1010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	0000	07-JAN-2011	
Quality Amendment (Response to Agency Questions)	0011	28-APR-2011	
Quality Amendment (Response to Agency Questions)	0016	08-JUN-2011	
Quality Amendment (Response to Agency Questions)	0019	13-JUN-2011	
Quality Amendment (Method Validation Reports)	0020	30-JUN-2011	
Amendment (Response to 05/11/2011 CMC IR)	0024	11-JUL-2011	
Quality Amendment (Response to Information Request)	0025	26-JUL-2011	
Quality Amendment (Response to Information Request)	0026	01-AUG-2011	
Quality Amendment (Response to Information Request)	0027	10-AUG-2011	
Quality Amendment (Response to Information Request)	0030	22-Aug-2011	
General Correspondence	0046	05-Dec-2011	
General Correspondence	0047	07-Dec-2011	
Resubmission/Class 1	0050	12-Jan-2012	

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck Sharp & Dohme Corp.
Address:	126 Lincoln Avenue
	P.O. Box 2000
	Mail Drop: RY33-204
	Rahway, NJ 07065-0900
Representative:	Chitkala Kalidas, Ph.D.
Telephone:	732-594-0599

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tafluprost
b) Non-Proprietary Name: Tafluprost
c) Code Name/# (ONDQA only): AFP-168
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: Prostaglandin analogue
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Sterile Ophthalmic Solution

12. STRENGTH/POTENCY: 0.0015%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __√__Rx ___OTC

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

_____SPOTS product – Form Completed

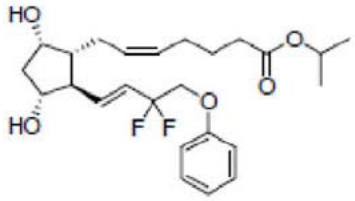
__√___Not a SPOTS product

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

Chemical Name: 1-methylethyl (5Z)-7-{(1R, 2R, 3R, 5S)-2-[(1E)-3,3-difluoro-4-phenoxy- 1-butenyl]-3,5-dihydroxycyclopentyl}-5-heptenoate
Molecular Formula: $C_{25}H_{34}F_2O_5$

Molecular Weight: 452.53

Chemical Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	7/25/2011 (M Zhou)	
	III			4	N/A	N/A	

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62690	Tafluprost
NDA	N/A	N/A

18. STATUS:

ONDQA: Approvable pending resolution of microbiology deficiencies.

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall Acceptable	13-Oct-2011	M Stock
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	N/A, according to the current ONDQA policy	N/A	N/A
DMEPA*	Zioptan is acceptable as the proprietary name	30-Aug-2011	D. Baugh
EA	Categorical exclusion is acceptable (see review)	25-Aug-2011	M Zhou
Microbiology	The application is recommended for approval	18-Jan-2011	J Cole

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 202-514

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. The 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 CMC Assessments

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

(1) General

NDA 202-514 is submitted by Merck Sharp & Dohme Corporation to seek approval of a preservative free formulation of 0.0015% tafluprost ophthalmic solution for the reduction of elevated intraocular pressure in open angle glaucoma and ocular hypertension. Tafluprost (MK-2452), a new molecular entity, is an analogue of prostaglandin F2α (PGF2α). Tafluprost is rapidly hydrolyzed by corneal esterases to the biologically active metabolite, tafluprost acid. Tafluprost 0.0015% preservative free (PF) and preservative containing (PC) formulations are currently approved in several other countries.

(2) Drug Substance

The drug substance, tafluprost, is a colorless to light yellow viscous liquid, with a molecular formula of $C_{25}H_{34}F_2O_5$ and a molecular weight of 453.53 Daltons. Tafluprost is a new molecular entity (NME) and it has not been previously marketed in the United States. Tafluprost is manufactured, controlled, packaged, and stability-tested at [redacted]. The information on manufacturing processes and controls for tafluprost is described in [redacted] DMF [redacted]. A letter of authorization to refer to DMF [redacted] was provided on behalf of [redacted] DMF [redacted] has been reviewed and all chemistry issues

have been resolved. As revised, the DMF is adequate to support the current NDA.

(3) Drug Product

The drug product, tafluprost 0.0015% ophthalmic solution is a sterile aqueous isotonic solution that contains the drug substance tafluprost and the excipients, sodium dihydrogen phosphate dihydrate, polysorbate 80, disodium edetate, glycerol, sodium hydroxide and/or hydrochloric acid, and water for injection. Glycerol is used to (b) (4) of the drug product. Sodium hydroxide and hydrochloric acid are used to adjust the solution pH to 5.5 – 6.7. All the excipients are of compendial grade (USP/NF).

The drug product solution is manufactured, (b) (4) by Laboratoire Unither, France. The drug product manufacturing process (b) (4) . Each single-use ampoule is filled with 0.3 mL of the sterile solution containing 4.5 µg of tafluprost and affixed with a label. The labeled ampoules are packed in (b) (4) pouches, 10 ampoules per pouch. The pouches are then packed in carton boxes. Commercial cartons are either 30-count (3 pouches) or 90-count (9 pouches) and sample cartons are 10-count (1 pouch).

At the time of the NDA submission, 18-month long term and 6-month accelerated stability data were provided from three registration stability batches. The stability testing of these batches is expected to continue to 36 months. In addition, 36-month long term and 6 month accelerated stability data from 3 batches were also provided. The available stability data support the proposed drug product shelf life of 36 months when stored in cold (2-8 ºC) protected from moisture. The single-dose ampoules have to be stored in the (b) (4) pouch to prevent water evaporation. The results from in-use studies support the proposed statement: (b) (4)

The applicant did not discuss their control strategy in the NDA. Based on this reviewer's evaluation of the NDA information, the following conventional control strategies are used for product quality assurance by the applicant and these appear to be adequate for product quality assurance.

- Use of excipients commonly used in ophthalmic products with excipient quality controlled by adherence to compendial specifications
- Use of critical process parameter ranges and in-process testing specification to control the manufacturing process
- Inclusion of secondary packaging for protection from light and water loss

- Release testing of final drug product for critical product attributes such as appearance, identity, osmolality, pH, assay, purity, sterility, endotoxin, and particulate matter.

During the first review cycle, the NDA as amended provided sufficient and adequate information on raw material controls, manufacturing processes and process controls, specifications for assuring consistent product quality of the drug substance and drug product, and sufficient stability information on the drug product to support the proposed expiry period. All facilities were found "Acceptable" by the Office of Compliance and all labels were reviewed and found to have the required information. The product quality microbiology reviewer, Dr. Jessica Cole, found the NDA deficient due to inappropriate sterility validation. This deficiency resulted in the NDA receiving an action of "Complete Response" the first review cycle. The complete response letter was issued on November 7, 2011. The NDA was resubmitted on January 13, 2012 with appropriate sterility validation data. This information was found satisfactory by the product quality microbiology reviewer, Dr. Jessica Cole, who has now recommended the NDA for approval. All pending CMC issues are now resolved.

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

Zioptan™ (tafluprost) is a sterile, preservative-free, clear, colorless, isotonic ophthalmic solution containing tafluprost 0.0015% (15 µg/mL) intended for topical administration to the eye. The recommended dose is one drop per affected eye once daily in the evening. The applicant seeks approval of tafluprost ophthalmic solution, 0.0015% for a once daily dosing regimen for the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.

C. Basis for Approvability or Not-Approval Recommendation

During the first review cycle, this NDA was recommended for approval in CMC Review #2 dated October 24, 2011, contingent upon satisfactory resolution of all pending product quality microbiology deficiencies. On January 13, 2012, the applicant filed a Class 1 resubmission with the requested quality microbiology data. The product quality microbiology reviewer, Dr. Jessica Cole, has reviewed the data and found the data acceptable. On January 17, 2012, Dr. Cole has recommended the application for approval in Product Quality Microbiology Review #3. As a result, all pending CMC issues have been resolved.

In summary, the NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, specifications, microbiology and endotoxin attributes and stability information to assure strength, purity, and quality of the drug product during the expiration dating period. All facilities have "Acceptable" site recommendations. All labels have the required information. Therefore, from the CMC perspective, NDA 202-514 is recommended for approval.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Maotang Zhou, Ph.D., Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Assessment II, ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

MAOTANG ZHOU
01/31/2012

RAPTI D MADURAWE
01/31/2012

MEMORANDUM

Date: November 1, 2011

To: NDA 202-514

From: Terrance Ocheltree, Ph.D., R.Ph.
Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 202-514, tafluprost ophthalmic solution, 0.0015%, ZIOPTAN™.

I have assessed the ONDQA reviews of NDA 202-514 by Maotang Zhou, Ph.D. The initial ONDQA CMC review was entered into DARRTS on August 26, 2011, with a recommendation for a Complete Response due to an absence of a recommendation from the Office of Compliance on the manufacturing and testing sites acceptability and pending labeling issues. A second CMC review was entered into DARRTS on October 24, 2011 by Dr. Zhou updating the status of the recommendation from the Office of Compliance and adding the recommendation of "Approvable pending resolution of microbiology deficiencies" from the Product Quality Microbiology Reviewer. On October 13, 2011 the Office of Compliance entered an Overall Recommendation of "Acceptable" into EES. However, due to the Product Quality Microbiology Review, the ONDQA recommendation remains Complete Response. An ONDQA Biopharmaceutics review was not performed for this NDA.

I concur with the determination that the information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product and support the recommendation of a drug product shelf life of 36 months for the proposed commercial product when it is stored in cold (2-8 ºC) environment and protected from moisture.

The Drug Master File (DMF) (b) (4) was reviewed for the drug substance, tafluprost, and found to be ADEQUATE on July 25, 2011 by Dr. Zhou to support This NDA

Secondary review of the CMC reviews was performed by Rapti Madurawe, Ph.D.

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

/s/

TERRANCE W OCHELTREE
11/07/2011

NDA 202-514

ZIOPTAN™ (tafluprost ophthalmic solution) 0.0015%

Merck Sharp & Dohme Co

Maotang Zhou, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V

CMC REVIEW OF NDA 202-514
For the Division of Transplant and Ophthalmology Products

CMC Review Data Sheet

1. NDA 202-514

2. REVIEW #: 2

3. REVIEW DATE: 17-Oct-2011

4. REVIEWER: Maotang Zhou, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 62,690 submission	23-May-2001
Original IND 62,690 CMC review	23-July-2001
End-of-phase-2 meeting (No CMC issues discussed)	24-Aug-2009
Pre-NDA meeting	13-Aug-1010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
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Quality Amendment (Response to Agency Questions)	0011	28-APR-2011	
Quality Amendment (Response to Agency Questions)	0016	08-JUN-2011	
Quality Amendment (Response to Agency Questions)	0019	13-JUN-2011	
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Quality Amendment (Response to Information Request)	0027	10-AUG-2011	
Quality Amendment (Response to Information Request)	0030	22-Aug-2011	

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck Sharp & Dohme Corp.
Address:	126 Lincoln Avenue
	P.O. Box 2000
	Mail Drop: RY33-204
	Rahway, NJ 07065-0900
Representative:	Chitkala Kalidas, Ph.D.
Telephone:	732-594-0599

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tafluprost
b) Non-Proprietary Name: Tafluprost
c) Code Name/# (ONDQA only): AFP-168
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: Prostaglandin analogue
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Sterile Ophthalmic Solution

12. STRENGTH/POTENCY: 0.0015%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __√__Rx ___OTC

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

_____SPOTS product – Form Completed

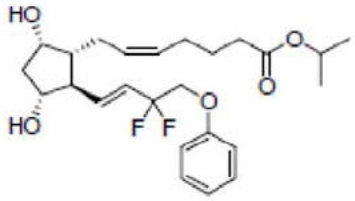
__√___Not a SPOTS product

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

Chemical Name: 1-methylethyl (5Z)-7-{(1R, 2R, 3R, 5S)-2-[(1E)-3,3-difluoro-4-phenoxy- 1-butenyl]-3,5-dihydroxycyclopentyl}-5-heptenoate
Molecular Formula: $C_{25}H_{34}F_2O_5$

Molecular Weight: 452.53

Chemical Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	7/25/2011 (M Zhou)	
	III			4	N/A	N/A	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
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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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62690	Tafluprost
NDA	N/A	N/A

18. STATUS:

ONDQA: Approvable pending resolution of microbiology deficiencies.

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall Acceptable	13-Oct-2011	M Stock
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	N/A, according to the current ONDQA policy	N/A	N/A
DMEPA*	Zioptan is acceptable as the proprietary name	30-Aug-2011	D. Baugh
EA	Categorical exclusion is acceptable (see review)	25-Aug-2011	M Zhou
Microbiology	Approvable pending resolution of microbiology deficiencies	30-Sep-2011	J Cole

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 202-514

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. However, the product quality microbiology reviewer has made the recommendation of "Approvable pending resolution of microbiology deficiencies". Therefore, from the CMC perspective, this NDA is not recommended for approval until all pending product quality microbiology deficiencies are satisfactorily resolved.

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

None

II. Summary of CMC Assessments

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

(1) General

NDA 202-514 is submitted by Merck Sharp & Dohme Corporation to seek approval of a preservative free formulation of 0.0015% tafluprost ophthalmic solution for the reduction of elevated intraocular pressure in open angle glaucoma and ocular hypertension. Tafluprost (MK-2452), a new molecular entity, is an analogue of prostaglandin F2α (PGF2α). Tafluprost is rapidly hydrolyzed by corneal esterases to the biologically active metabolite, tafluprost acid. Tafluprost 0.0015% preservative free (PF) and preservative containing (PC) formulations are currently approved in several other countries.

(2) Drug Substance

The drug substance, tafluprost, is a colorless to light yellow viscous liquid, with a molecular formula of $C_{25}H_{34}F_2O_5$ and a molecular weight of 453.53 Daltons. Tafluprost is a new molecular entity (NME) and it has not been previously marketed in the United States. Tafluprost is manufactured, controlled, packaged, and stability-tested at (b) (4) The information on manufacturing processes and controls for tafluprost is described in (b) (4) DMF

(b) (4) A letter of authorization to refer to DMF (b) (4) was provided on behalf of (b) (4) DMF (b) (4) has been reviewed and all chemistry issues have been resolved. As revised, the DMF is adequate to support the current NDA.

(3) Drug Product

The drug product, tafluprost 0.0015% ophthalmic solution is a sterile aqueous isotonic solution that contains the drug substance tafluprost and the excipients, sodium dihydrogen phosphate dihydrate, polysorbate 80, disodium edetate, glycerol, sodium hydroxide and/or hydrochloric acid, and water for injection. Glycerol is used to (b) (4) of the drug product. Sodium hydroxide and hydrochloric acid are used to adjust the solution pH to 5.5 – 6.7. All the excipients are of compendial grade (USP/NF).

The drug product solution is manufactured, (b) (4) by Laboratoire Unither, France. The drug product manufacturing process (b) (4)

(b) (4)

(b) (4) Each single-use ampoule is filled with 0.3 mL of the sterile solution containing 4.5 µg of tafluprost and affixed with a label. The labeled ampoules are packed in (b) (4) pouches, 10 ampoules per pouch. The pouches are then packed in carton boxes. Commercial cartons are either 30-count (3 pouches) or 90-count (9 pouches) and sample cartons are 10-count (1 pouch).

At the time of the NDA submission, 18-month long term and 6-month accelerated stability data were provided from three registration stability batches. The stability testing of these batches is expected to continue to 36 months. In addition, 36-month long term and 6 month accelerated stability data from 3 batches were also provided. The available stability data support the proposed drug product shelf life of 36 months when stored in cold (2-8 °C) protected from moisture. The single-dose ampoules have to be stored in the (b) (4) pouch to prevent water evaporation. The results from in-use studies support the proposed statement: (b) (4)

The applicant did not discuss their control strategy in the NDA. Based on this reviewer's evaluation of the NDA information, the following conventional control strategies are used for product quality assurance by the applicant and these appear to be adequate for product quality assurance.

- Use of excipients commonly used in ophthalmic products with excipient quality controlled by adherence to compendial specifications
- Use of critical process parameter ranges and in-process testing specification to control the manufacturing process

- Inclusion of secondary packaging for protection from light and water loss
- Release testing of final drug product for critical product attributes such as appearance, identity, osmolality, pH, assay, purity, sterility, endotoxin, and particulate matter.

During review, discrepancies were noted in some data and information provided in the NDA. Additional information provided by the applicant relating to these issues was reviewed, and as presented, is satisfactory. The CMC information as provided in the NDA is adequate to assure the identity, strength, purity and quality of the drug product. On September 30, 2011, the product quality microbiology reviewer made the recommendation of "Approvable pending resolution of microbiology deficiencies". Therefore, from the CMC perspective, this NDA is not recommended for approval until all pending product quality microbiology deficiencies are satisfactorily resolved.

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

Zioptan™ (tafluprost) is a sterile, preservative-free, clear, colorless, isotonic ophthalmic solution containing tafluprost 0.0015% (15 µg/mL) intended for topical administration to the eye. The recommended dose is one drop per affected eye once daily in the evening. The applicant seeks approval of tafluprost ophthalmic solution, 0.0015% for a once daily dosing regimen for the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.

C. Basis for Approvability or Not-Approval Recommendation

In CMC review #1 dated August 25, 2011, this NDA was recommended for approval contingent upon the following pending issues being satisfactorily resolved: (1) Overall site recommendation: Office of Compliance has not yet issued an overall acceptable site recommendation in EES; (2) Labeling: The review team has not yet initiated labeling negotiations

On October 13, 2011, the Office of Compliance made an overall recommendation of "Acceptable" for the facilities related to the NDA (See the attached establish evaluation report). The labeling changes recommended by ONDQA have been forwarded to the applicant by the FDA review team (See CMC Assessment in this review). However, on September 30, 2011, the product quality microbiology reviewer made the recommendation of "Approvable pending resolution of microbiology deficiencies" (See Dr. Jessica Cole's Product Quality Microbiology Review in DARRTS). Therefore, from the CMC perspective, this NDA is not recommended for approval until all pending product quality microbiology deficiencies are satisfactorily resolved.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Maotang Zhou, Ph.D., Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Assessment II, ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

MAOTANG ZHOU
10/17/2011

RAPTI D MADURAWE
10/24/2011

NDA 202-514

ZIOPTAN™ (tafluprost ophthalmic solution) 0.0015%

Merck Sharp & Dohme Co

Maotang Zhou, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V

CMC REVIEW OF NDA 202-514
For the Division of Transplant and Ophthalmology Products

Table of Contents

CMC Review Data Sheet

1. NDA 202-514

2. REVIEW #: 1

3. REVIEW DATE: 25-Aug-2011

4. REVIEWER: Maotang Zhou, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 62,690 submission	23-May-2001
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Quality Amendment (Response to Information Request)	0025	26-JUL-2011	
Quality Amendment (Response to Information Request)	0026	01-AUG-2011	
Quality Amendment (Response to Information Request)	0027	10-AUG-2011	

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck Sharp & Dohme Corp.
Address:	126 Lincoln Avenue
	P.O. Box 2000
	Mail Drop: RY33-204
	Rahway, NJ 07065-0900
Representative:	Chitkala Kalidas, Ph.D.
Telephone:	732-594-0599

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tafluprost
b) Non-Proprietary Name: Tafluprost
c) Code Name/# (ONDQA only): AFP-168
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: Prostaglandin analogue
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Sterile Ophthalmic Solution

12. STRENGTH/POTENCY: 0.0015%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __√__Rx ___OTC

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

_____SPOTS product – Form Completed

__√__Not a SPOTS product

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

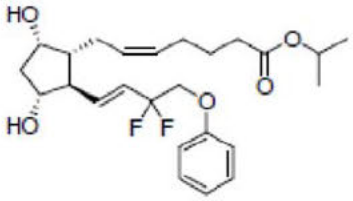
Chemical Name: 1-methylethyl (5Z)-7-{(1R, 2R, 3R, 5S)-2-[(1E)-3,3-difluoro-4-phenoxy- 1-butenyl]-3,5-dihydroxycyclopentyl}-5-heptenoate

CMC Review Data Sheet

Molecular Formula: $C_{25}H_{34}F_2O_5$

Molecular Weight: 452.53

Chemical Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	7/25/2011 (M Zhou)	
	III			4	N/A	N/A	

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62690	Tafluprost
NDA	N/A	N/A

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA*	N/A		
EA	Categorical exclusion (see review)	8/25/2011	M Zhou
Microbiology	N/A		

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 202-514

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product. However, a recommendation from the Office of Compliance on the site acceptability has not been made as of the date of this review and the labeling is pending team review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all pending issues are satisfactorily resolved.

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

None

II. Summary of CMC Assessments

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

(1) General

NDA 202-514 is submitted by Merck Sharp & Dohme Corporation to seek approval of a preservative free formulation of 0.0015% tafluprost ophthalmic solution for the reduction of elevated intraocular pressure in open angle glaucoma and ocular hypertension. Tafluprost (MK-2452), a new molecular entity, is an analogue of prostaglandin F2α (PGF2α). Tafluprost is rapidly hydrolyzed by corneal esterases to the biologically active metabolite, tafluprost acid. Tafluprost 0.0015% preservative free (PF) and preservative containing (PC) formulations are currently approved in several other countries.

(2) Drug Substance

The drug substance, tafluprost, is a colorless to light yellow viscous liquid, with a molecular formula of $C_{25}H_{34}F_2O_5$ and a molecular weight of 453.53 Daltons. Tafluprost is a new molecular entity (NME) and it has not been previously marketed in the United States. Tafluprost is manufactured, controlled, packaged, and stability-tested at (b) (4) (b) (4) The information on manufacturing processes and controls for tafluprost is described in (b) (4) DMF (b) (4). A letter of authorization to refer to DMF (b) (4) was provided on behalf of (b) (4). DMF (b) (4) has been reviewed

and all chemistry issues have been resolved. As revised, the DMF is adequate to support the current NDA.

(3) Drug Product

The drug product, tafluprost 0.0015% ophthalmic solution is a sterile aqueous isotonic solution that contains the drug substance tafluprost and the excipients, sodium dihydrogen phosphate dihydrate, polysorbate 80, disodium edetate, glycerol, sodium hydroxide and/or hydrochloric acid, and water for injection. Glycerol is used to (b) (4) (b) (4) of the drug product. Sodium hydroxide and hydrochloric acid are used to adjust the solution pH to 5.5 – 6.7. All the excipients are of compendial grade (USP/NF).

The drug product solution is manufactured, (b) (4) by Laboratoire Unither, France. The drug product manufacturing process (b) (4) (b) (4) (b) (4) Each single-use ampoule is filled with 0.3 mL of the sterile solution containing 4.5 µg of tafluprost and affixed with a label. The labeled ampoules are packed in (b) (4) pouches, 10 ampoules per pouch. The pouches are then packed in carton boxes. Commercial cartons are either 30-count (3 pouches) or 90-count (9 pouches) and sample cartons are 10-count (1 pouch).

At the time of the NDA submission, 18-month long term and 6-month accelerated stability data were provided from three registration stability batches. The stability testing of these batches is expected to continue to 36 months. In addition, 36-month long term and 6 month accelerated stability data from 3 batches were also provided. The available stability data support the proposed drug product shelf life of 36 months when stored in cold (2-8 °C) protected from moisture. The single-dose ampoules have to be stored in the (b) (4) pouch to prevent water evaporation. The results from in-use studies support the proposed statement: (b) (4) (b) (4)

The applicant did not discuss their control strategy in the NDA. Based on this reviewer's evaluation of the NDA information, the following conventional control strategies are used for product quality assurance by the applicant and these appear to be adequate for product quality assurance.

- Use of excipients commonly used in ophthalmic products with excipient quality controlled by adherence to compendial specifications
- Use of critical process parameter ranges and in-process testing specification to control the manufacturing process
- Inclusion of secondary packaging for protection from light and water loss
- Release testing of final drug product for critical product attributes such as appearance, identity, osmolality, pH, assay, purity, sterility, endotoxin, and particulate matter.

During review, discrepancies were noted in some data and information provided in the NDA. Additional information provided by the applicant relating to these issues was reviewed, and as presented, is satisfactory. The CMC information as provided in the NDA is adequate to assure the identity, strength, purity and quality of the drug product. However, a recommendation from the Office of Compliance on the site acceptability has not been made as of the date of this review and the labeling is pending team review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all pending issues are resolved.

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

Zioptan™ (tafluprost) is a sterile, preservative-free, clear, colorless, isotonic ophthalmic solution containing tafluprost 0.0015% (15 µg/mL) intended for topical administration to the eye. The recommended dose is one drop per affected eye once daily in the evening. The applicant seeks approval of tafluprost ophthalmic solution, 0.0015% for a once daily dosing regimen for the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, adequate specifications, and stability data for assuring consistent product quality of the drug substance and drug product. The quality microbiology reviewer has found the microbiology and endotoxin control of the drug product satisfactory. Prior to approval, the following pending issues must be satisfactorily resolved.

- Overall site recommendation: Office of Compliance has not yet issued an overall acceptable site recommendation in EES.
- Labeling: The review team has not yet initiated labeling negotiations

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Maotang Zhou, Ph.D., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Assessment II, ONDQA

C. CC Block: entered electronically in DARRTS

67 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MAOTANG ZHOU
08/26/2011

RAPTI D MADURAWE
08/26/2011

Initial Quality Assessment
Branch __IV__
Pre-Marketing Assessment Division __II__

OND Division:	Division of Anti-Infective and Ophthalmology Produ
NDA:	202-514
Applicant:	Merck Sharp & Dohme Corp
Stamp Date:	January 7, 2011
PDUFA Date:	November 7, 2011
Trademark:	Saflutan
Established Name:	tafluprost ophthalmic solution, 0.0015%
Dosage Form:	Ophthalmic Solution
Route of Administration:	Topical
Indication:	Reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension
PAL:	Linda Ng, Ph.D.

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☐

Summary and Critical Issues:

Summary

Saflutan (tafluprost ophthalmic solution) 0.0015% is a 1S NDA, dated January 7, 2011, by eCTD format, accepted for standard review. Tafluprost, also known as MK-2452 within Merck, is a prostaglandin. The product is a preservative-free unit dose in one strength and size for the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension. The applicant states that it is generally believed that prostaglandin analogues reduce intraocular pressure by increasing uveoscleral outflow of aqueous humor. The related IND number is 62,690.

A microbiology consult was submitted by the OND PM, Constantine Markos and Dr. Jessica Cole was assigned. The trade name consult was sent directly from the applicant to OSE. The EES evaluation was performed by ONDQA PM Althea Cuff who confirmed sites with the applicant and finalized the request with the CMC reviewer Dr. Maotang Zhou.

The drug substance section was not submitted. The applicant was advised to submit minimal information even when the drug substance is referenced to a DMF. DMF (b) (4) from (b) (4) contained information on tafluprost. The letter of authorization was dated December 17, 2010. The drug substance section was amended on February 9, 2011 to contain general information and the acceptance specification sheet with history of changes for the specification.

The drug substance, tafluprost, is manufactured by [redacted] with all information submitted in DMF [redacted]. Very minimal information on tafluprost, a new molecular entity, was submitted to the NDA. Comments on the DMF [redacted] will be conveyed to the reviewer due to confidentiality.

The drug product, at pH of 5.5 to 6.7, and osmolality of 260 to 300 mOsm/kg, contains glycerol [redacted], disodium edentate [redacted], polysorbate 80 [redacted], and sodium dihydrogen phosphate dehydrate [redacted]. The product is manufactured, [redacted] at Laboratoire Unither, France. Stability testing will be performed at [redacted]. A [redacted] low-density polyethylene (LDPE) [redacted] container.

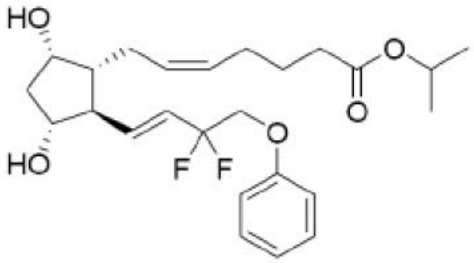
The drug product, 0.3 mL fill size, is [redacted] filled in a [redacted] LDPE vial. [redacted]

The physician sample is the same as the trade sample. The physician sample consists of 10 vials, [redacted], in a pouch whereas the trade product consists of either 30 vials or 90 vials in pouches per trade carton.

Studies related to stress under ICH light conditions, water loss, and in-use, were performed. No comparability protocol submitted.

The commercial batch size is claimed to be [redacted]. The stability data included 3 commercial strength batches at market site for up to 18 months at 5ºC/ambient humidity and accelerated condition of 20ºC/40%RH. Support stability data for 36 months were submitted from an alternate site, [redacted]. An expiry of 36 months is claimed. Product is claimed for storage under refrigeration.

Structural Formula:



Molecular weight: 452.53

Molecular formula: C25H34F2O5

Critical issues for review

- The drug substance is a new molecular entity. Since most information is submitted to the DMF, comments have been and will be conveyed directly to the reviewer.
- The reference standard in the drug product section is claimed to be submitted in 3.2.S.5 – 2452-ophsln. No such section exists. Reviewer should follow up.
- All tests should be evaluated for meaningful conditions and criteria for both drug substance and drug product. In the drug substance specification, the "Any individual unspecified impurity" instead of "Others" should be used.
- The LDPE (b) (4) are described with the word 'or equivalent'. Leachables could be different with different components. The applicant should be made aware.
- The post approval commitment does not contain language to inform the division in case of failure and to meet 21 CFR 314.81(b)(1). Current statement is not adequate.
- In the drug product specification, Table II of USP <789> for particulate matter testing should be adopted and impurities reporting should follow ICH Q3B format.
- Note that endotoxin testing is missing in the drug product specification. This may be a micro issue.
- Recommended that the (b) (4) be evaluated.
- Does not appear to have any freeze-thaw study for the drug product. Such study should be performed.
- The analytical procedure for assay and impurities is recommended to contain a chromatogram that includes labeled impurities; system suitability to include a standard at the quantitation limit to ensure detectability of impurities observed at that level.
- The dp specification in the methods validation package does not appear to the same as in the dp section. Reviewer should follow up.
- Not clear if a leachable study is performed. Somewhere it is stated that leachable was observed at (b) (4). No leachable was included in the drug product specification. Reviewer should follow up.
- Labeling include instructions to patients as well as the package insert. Suggest to use the word (b) (4) to described the container in the How Supplied section. Reviewer should review all labeling for adequacy.

- Comments for 74-Day Letter

None recommended at this time.

D. Review, Comments and Recommendation:

Acceptable for filing. Dr. Maotang Zhou has been assigned to review this NDA.

_____Linda Ng, Ph.D._____ _____ _
CMC Lead Date

___Stephen Miller, Ph.D._____ _____
Acting Branch Chief Date

Cc: OND PM CMarkos
ONDQA PM ACuff

Appendix 1. Composition of the Drug Product

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Composition of Tafluprost 15 microg/mL Eye Drops in Single-Dose Container.

Drug substance	Reference	Percent (w/v)	Quantity (mg/mL)	Function
Tafluprost	In-house[†]	0.0015	0.015	Drug substance
Excipients				(b) (4)
Glycerol	PhEur/USP			
Sodium dihydrogen phosphate dihydrate	PhEur/USP			
Disodium edetate	PhEur/USP			
Polysorbate 80	PhEur			
Sodium hydroxide[‡] and/or	PhEur/USP	q.s.	q.s.[§]	pH adjuster
hydrochloric acid, concentrated[‡]	PhEur	q.s.	q.s.[§]	pH adjuster
Water for injection	PhEur			(b) (4)
(b) (4)				
				(b) (4)

Appendix 2. Drug Substance Specification

Current Specifications of Tafluprost Drug Substance

Test	Specification
Description	Colorless to light yellow viscous liquid
Identification/infared spectroscopy	Corresponds to reference spectrum
Identification/optical rotation	(b) (4)
Clarity of solution	
Related substances	
Residual solvents	
Water content	
Assay	
Enantiomeric impurity (in-house specification)	
Microbial limit	

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Appendix 3. Drug Product Specification

5.1 Release and Shelf Life Specifications

Table 3.2.P.5.1-2452-ophsln: 1

Specification Established for Tafluprost Ophthalmic Solution

Test Items	Requirements	Test Methods
Appearance	Clear, colorless solution. Practically free from visible particles.	Test by visual observation and Sec 3.2.P.5.2.1-2452-ophsln
Identification/ HPLC, UV/ Tafluprost[†]	UV spectrum is similar to the result of reference standard; retention time is within ± 5% of reference standard	Identification, Assay and Related Substances Sec. 3.2.P.5.2.4-2452-ophsln
pH	5.5 – 6.7	Sec 3.2.P.5.2.2-2452-ophsln
Osmolality	260 – 300 mOsm/kg	Sec 3.2.P.5.2.3-2452-ophsln
Impurities/Degradates/ HPLC/ Tafluprost	(b) (4)	
Assay/ HPLC/ Tafluprost		
Sterility		
Particulate Matter (light Obscuration/Microscopy)		
	(b) (4)	

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

/s/

LINDA L NG
04/21/2011

STEPHEN P MILLER
04/25/2011

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 202514/000	**Action Goal:**	
Star te:	07-JAN-2011	**District Goal:**	08-SEP-2011
Regulatory:	07-NOV-2011		
Applicant:	MERCK SHARP DOHME	**Brand Name:**	Tafluprost
	126 EAST LINCOLN AVE RY 33 212	**Estab. Name:**	
	RAHWAY, NJ 070650900	**Generic Name:**	
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	590	001; DROPS; TAFLUPROST; .0015%	

Application Comment:

FDA Contacts:	A. CUFF	Project Manager	(HF-01)		301-796-4061
	L. NG	Team Leader			301-796-1426

Overall Recommendation:	ACCEPTABLE	on 13-OCT-2011	by M. STOCK	(HFD-320)	301-796-4753
	PENDING	on 22-JUL-2011	by EES_PROD		
	WITHHOLD	on 27-JUN-2011	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: DRUG SUBSTANCE MANUFACTURING, PACAKGING AND RELEASEAND STABILITTY TESTING SITE (b) (4)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	(b) (4)				CUFFA
SUBMITTED TO OC					CUFFA
SUBMITTED TO DO		Product Specific			TOULOUSEM
ASSIGNED INSPECTION TO IB		Product Specific			PHILPYE
INSPECTION PERFORMED					CARL.LEE
AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED					
UN REVIEW	30-SEP-2011				STOCKM
DO RECOMMENDATION	13-OCT-2011			ACCEPTABLE INSPECTION	STOCKM
OC RECOMMENDATION	13-OCT-2011			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURING, PACKAGING AND RELEASE TESTING SITE (b) (4)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
SUBMITTED TO OC	(b) (4)				CUFFA
SUBMITTED TO DO NEW FIRM		Product Specific			TOULOUSEM
ASSIGNED INSPECTION TO IB FD PILOT JOINT INSPECTION POTENTIAL		Product Specific			PHILPYE
INSPECTION SCHEDULED	(b) (4)		17-MAY-2011		IRIVERA
INSPECTION PERFORMED			16-MAY-2011		DEBRA.LOVE

was a NDA Pre-Approval Inspection of a drug manufacturer (FACTS assignment ID # (b) (4), initiated in response to a CDER EES Request for Inspection for NDA # 202514/000, for Tafluprost Drops 0.0015%. The applicant is Merck Sharp Dome, 126 East Lincoln Ave., Rahway, NJ 07065. Laboratoire Unither, Coutances, France is identified in the NDA as the finished dosage manufacturer, (b) (4). Laboratoire Unither does not currently manufacture any prescription drug products for export to the U.S. (b) (4)

The inspection covered NDA # 202514/000, for Tafluprost Drops 0.0015% and was conducted in accordance with Compliance Programs 7346.832 Pre-Approval Inspections, 7356.002A, Sterile Drug Manufacturing Inspections, and 7356.002 Drug Manufacturing Inspections.

This was the first inspection of the firm.

On (b) (4), Investigator (b) (4) and Microbiologist (b) (4) presented credentials to (b) (4). The current inspection covered Tafluprost 0.0015% eye drops in single-dose container which was developed for the topical treatment of intraocular pressure. At the conclusion of the inspection on (b) (4), an 8-point FDA-483 was issued to (b) (4). The observations cited included the following.

1. (b) (4)

DO RECOMMENDATION	22-JUL-2011	ACCEPTABLE INSPECTION	STOCKM
OC RECOMMENDATION	25-JUL-2011	ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** 3002807653

MERCK SHARP DOHME

SHOTTEN LANE
CRAMLINGTON, , UNITED KINGDOM

DMF No: **AADA:**

Responsibilities: (b) (4)

Establishment Comment: DRUG PRODUCT (b) (4) TESTING: FOR THE ANNUAL BATCHES MANUFACTURED AT LABORATORIE UNITHER (on (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	(b) (4)				CUFFA
OC RECOMMENDATION				ACCEPTABLE	SMITHDE
				BASED ON PROFILE	

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202-514 (ONDQA)

NDA Number: 202-514

Established/Proper Name: Saflutan (tafluprost ophthalmic solution) 0.0015%

Applicant: Merck Sharp & Dohme Co

Letter Date: January 7, 2011

Stamp Date: January 7, 2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		eCTD with missing drug substance sections
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		Seems to be

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		Submitted in section 1.1.2
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			N/A

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		Clarification made via communication between ONDQA PM and applicant. The facility site address is different between the NDA and DMF.
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		Minor clarification made via communication between ONDQA PM and applicant.

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		Submitted in 1.1.2

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	x		Section 1.12.14

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202-514 (ONDQA)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?		x	Just reference DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Located in DMF (b) (4); Applicant has been informed to submit appropriate info to the NDA. Sections submitted in amendment.
14.	Does the section contain information regarding the characterization of the DS?		x	
15.	Does the section contain controls for the DS?		x	
16.	Has stability data and analysis been provided for the drug substance?		x	
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			Not obvious in the NDA
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			Not obvious in the NDA

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		Tafluprost ophthalmic solution manufactured at Laboratoire Unither, France.
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		Executed batch records for (b) (4) filling submitted. Section.3.2.R.1.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	Not needed for an Ophthalmic solution
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		3 batches of commercial strength at market site for up to 18 months at 5ºC ambient humidity and accelerated temperature at 25ºC/40%RH were submitted. Commercial strength at (b) (4) alternate site, for 36 months submitted. Requested 36 months expiry
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			Not obvious

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202-514 (ONDQA)

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		Included. Section 3.2.R.2

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	x		Incorporated in various part of the NDA including Section 3.2.P.3.5

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Tafluprost	12/17/10	
	III		(b) (4)	11/10/10	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		Mock up for carton, sample and trade

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		Information for the missing ds section was asked and submitted/

35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?			Very likely

{See appended electronic signature page}

Linda Ng, Ph.D.
CMC Lead
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Stephen Miller, Ph.D.
Acting Branch Chief
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

cc: OND PM CMarkos
ONDQA PM ACuff
CMC Reviewer MZhou

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202-514 (ONDQA)

Chemistry comment forwarded by ONDQA PM to the applicant:

Although you are referencing DMF [redacted] (b) (4) for drug substance information, in order to facilitate our review please provide important CMC information in Sections 2.3.S and 3.2.S of the NDA. Please include established name, structure, acceptance specification for the drug substance, and information about drug substance attributes which are important for the drug product manufacture and product performance.

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

/s/

LINDA L NG
02/08/2011

STEPHEN P MILLER
02/14/2011