CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202211s000

CHEMISTRY REVIEW(S)

NDA 202211
ADDENDUM

Oxytrol for Women (oxybutynin transdermal system)

MSD Consumer Care, Inc.

Drug Substance Review: Sheldon Markofsky, Ph.D.
Branch VII
DNDQA III/ONDQA

Drug Product Review: Caroline Strasinger, Ph.D.
Branch IV
DNDQA II/ONDQA

CMC Review of NDA 202211
For the DNCE

Chemistry Review Data Sheet

1. NDA 202211

2. REVIEW #: #2

3. REVIEW DATE: 21-DEC-2012

4. REVIEWER: Caroline Strasinger, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	
Quality Review #1	16-NOV-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	26-MAR-2012
Amendment	29-AUG-2012
Amendment	31-AUG-2012
Amendment	09-OCT-2012
Amendment	04-DEC-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	MSD Consumer Care, Inc.
Address:	556 Morris Avenue Summit, NJ 07901
Representative:	Nancy Pierro
Telephone:	908-473-5709

The Chemistry Review for NDA 202211

The Executive Summary

I. Synopsis of Addendum

The original Quality Review recommended complete response from the CMC perspective based on an inadequate acceptance criterion for the presence of (b) (4) label and labeling deficiencies and the overall office of compliance recommendation. All issues have been resolved and the application is now recommended for Approval from the CMC perspective.

Additionally, a minor amendment was made on 04-DEC-2012 to update the stability protocol and acknowledge a shelf-life of 24 months. Details are discussed in the Reviewer Notes below.

II. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has issued an "***ACCEPTABLE***" overall recommendation on all the manufacturing facilities.

The labels/labeling have adequate information.

Therefore, from the ONDQA perspective, this NDA is recommended for **APPROVAL**.

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

Per DMEPA request a PMC has been agreed upon between the Applicant and Agency in a teleconference on November 15, 2012. The Applicant has committed to changing the text on the backing film to a darker ink within one year from the date of approval. Although this is a PMC initiated by DMEPA, a change in ink will require CMC review when the submission for the new ink arrives; as such the PMC is noted in this review addendum.

Chemistry Assessment

Background
This addendum to the Quality Review dated 16-NOV-2012 addresses the following:

- Revision of the recommendation on the (b) (4) specification
- Stability protocol amendment dated 4-DEC-2012
- Label/Labeling communication
- Change in overall recommendation from compliance and updated EES report

(b) (4) Specification and Acceptance Criteria

The discussion of (b) (4) in section P.5.6 and the reviewer evaluation for P.5.6 in the original review dated 16-NOV-2012 should be changed to the following.

(b) (4)
As a post approval commitment for the European market, the Oxybutynin Transdermal System's manufacturer developed a method and specification for (b) (4) examination. Originally a limit of NMT (b) (4) of label claim was proposed, however after feed back from the European Medicines Agency (EMA) a limit of NMT (b) (4) label claim was implemented. It is proposed to the use the same specification and acceptance criterion for the Oxytrol OTC product. 85 batches were subjected to (b) (4) examination (1905 systems) were tested at both release and stability. (b) (4) ranging in size from (b) (4) were observed in approximately 1% of all systems examined, most of which were development batches; of the 57 commercial batches subjected to (b) (4) examination only 4 (b) (4) were observed. Since implementation of the method an additional 7 batches have been placed on stability and no (b) (4) have been observed.

The Applicant states that due to the infrequency and size of oxybutynin (b) (4) the presence of (b) (4) would have no impact on in-vitro or in-vivo drug product performance, even if it is assumed that the oxybutynin present in (b) (4) form is unavailable for in-vitro release or in-vivo absorption. The Applicant has provided in-vitro release data to support this claim. Additionally, all observation show that when using worst case calculations (assuming a (b) (4) no more than (b) (4) of the oxybutynin content is in (b) (4) form and the acceptance criterion of NMT (b) (4) is tighter than for that of assay of ±10%.

Reviewer Comment: Based on the historical data provided, the justification that (b) (4) (b) (4) presence does not impact delivery of the drug substance, and the use of the method by the EMA the method and acceptance criterion for (b) (4) is appropriate.

Reviewer Evaluation: Justification for specification is adequate.

Stability Protocol

The stability protocol was updated to include tests for [redacted] (b) (4) and [redacted] (b) (4) observation. The new protocol provided on 5-DEC-2012 can be seen below.

TABLE 1
INITIAL STABILITY PROTOCOL FOR OXYBUTYNIN TRANSDERMAL SYSTEM 3.9 mg/day

Test	Initial	Time (months)/Stability Condition																
		1		2		3			6			9		12		18	24	36
		30H	40H	30H	40H	25H	30H	40H	25H	30H	40H	25H	30H	25H	30H	25H	25H	25H
Appearance	X	O	X	O	X	X	O	X	X	O	X	X	O	X	O	X	X	X
[redacted] (b) (4)	X	O	X	O	X	X	O	X	X	O	X	X	O	X	O	X	X	X
Qualitative Quantitative	X	O	X	O	X	X	O	X	X	O	X	X	O	X	O	X	X	X
Oxybutynin Assay	X	O	X	O	X	X	O	X	X	O	X	X	O	X	O	X	X	X
Degradation Products	X	O	X	O	X	X	O	X	X	O	X	X	O	X	O	X	X	X
Triacetin Content	X	O	X	O	X	X	O	X	X	O	X	X	O	X	O	X	X	X
Drug Release	X	O	X	O	X	X	O	X	X	O	X	X	O	X	O	X	X	X
Release Liner Peel	X	O	X	O	X	X	O	X	X	O	X	X	O	X	O	X	X	X
90° Adhesion	X	O	X	O	X	X	O	X	X	O	X	X	O	X	O	X	X	X
[redacted] (b) (4)	X	O	X	O	X	X	O	X	X	O	X	X	O	X	O	X	X	X
[redacted] (b) (4)	X	O	X	O	X	X	O	X	X	O	X	X	O	X	O	X	X	X
[redacted] (b) (4)	X	O	X	O	X	X	O	X	X	O	X	X	O	X	O	X	X	X

X = Test Performed
O = Optional testing on stored samples
Storage Conditions: 25H = 25°C±2°C / 60%±5% Relative Humidity
30H = 30°C±2°C / 65%±5% Relative Humidity
40H = 40°C±2°C / 75%±5% Relative Humidity

Reviewer Evaluation: The information is adequate.

Label/Labeling

CMC related label/labeling comments were communicated to the Applicant on 20-DEC-2012.

It was agreed upon within the division that the word "Patch" would only be used on the patient instruction panels and information leaflet. The Primary Display Panel and pouch (immediate container closure) will utilize the words "transdermal system." The word patch should be introduced in the patient instruction information as "transdermal system (patch)." Thereafter only the term patch is required. This presentation is consistent with the Rx product.

Because this is an OTC product, the word Patch was utilized in patient use studies, and to be consistent with the Rx product, the use of the word Patch is acceptable in patient instruction portions of the label.

Reviewer Evaluation: The label/labeling is adequate.

Office of Compliance Recommendation

The Office of Compliance issued an overall "ACCEPTABLE" recommendation for all facilities involved in the manufacture and testing of the drug product on 21-DEC-2012. The updated EES report follows.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 202211/000	**Sponsor:**	MSD CONSUMER
Org. Code:	560		556 MORRIS AVE
Priority:	8		SUMMIT, NJ 07901
Stamp Date:	26-MAR-2012	**Brand Name:**	Oxytrol for Women
PDUFA Date:	26-JAN-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	OXYBUTYNIN TRANSDERMAL SYSTEM 3.9 MG/DAY
District Goal:	27-NOV-2012	**Product Number; Dosage Form; Ingredient; Strengths**	001; PATCH; OXYBUTYNIN; 3.9MG

FDA Contacts:	Y. LIU	Project Manager	3017961926
	S. MARKOFSKY	Review Chemist	3017961412
	S. DE	Team Leader	3017961664

Overall Recommendation:	ACCEPTABLE	on 21-DEC-2012	by M. STOCK	(HFD-320)	3017964753
	PENDING	on 13-DEC-2012	by EES_PROD		
	PENDING	on 23-OCT-2012	by EES_PROD		
	ACCEPTABLE	on 29-JUN-2012	by EES_PROD		
	PENDING	on 13-APR-2012	by EES_PROD		
	PENDING	on 13-APR-2012	by EES_PROD		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	(b) (4)
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-APR-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

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

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-APR-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-APR-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-JUN-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-APR-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-APR-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** 1722262 **FEI:** 1000117147
WATSON LABORATORIES INC

SALT LAKE CITY, , UNITED STATES 841081222

DMF No: **AADA:**

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

Profile: TRANSDERMAL PATCH **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-DEC-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

CAROLINE STRASINGER
12/21/2012

TERRANCE W OCHELTREE
12/21/2012

NDA 202-211

Oxytrol for Women
Oxybutynin Transdermal System

MSD Consumer Care, Inc.

Drug Substance Review: Sheldon Markofsky, Ph.D.
Branch VII
DNDQA III/ONDQA

Drug Product Review: Caroline Strasinger, Ph.D.
Branch IV
DNDQA II/ONDQA

CMC Review for
Division of NCE

Table of Contents

Chemistry Review Data Sheet

1. NDA 202-211

2. REVIEW #: #1

3. REVIEW DATE: November 13, 2012

4. REVIEWER: Sheldon Markofsky, Ph.D; Caroline Strasinger, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	26-MAR-2012
Amendment	29-AUG-2012
Amendment	31-AUG-2012
Amendment	09-OCT-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	MSD Consumer Care, Inc.
Address:	556 Morris Avenue Summit, NJ 07901
Representative:	Nancy Pierro
Telephone:	908-473-5709

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

a) Proprietary Name: Oxytrol for Women
b) Non-Proprietary Name (USAN): oxybutynin transdermal system
c) Code Name/#: N/A
d) Chem. Type/Submission Priority:
- Chem. Type: 3
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: over the counter relief of symptoms of over-active bladder in adult women

11. DOSAGE FORM: Transdermal System

12. STRENGTH/POTENCY: 3.9 mg/day; Twice weekly wear period

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __Rx _X_OTC

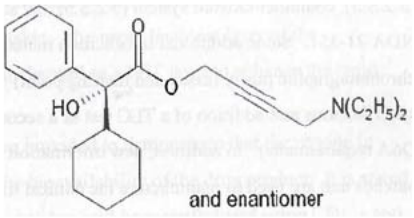
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Oxybutynin:

4-(Diethylamino)-2-butyn-1-yl-phenylcyclohexylglycolate
Molecular formula: $C_{22}H_{31}N0_3$
Molecular Weight: 357.49



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Oxybutynin Base	1	Adequate	8/10/2012	Dr. S. Markofsky for NDA 202-211
	IV		(b) (4)	4/7	N/A		(b) (4) approved for Rx product
	IV			4/7	N/A		(b) (4) approved for Rx product
	IV			4/7	N/A		(b) (4) approved for Rx product
	IV			4/7	N/A		(b) (4) approved for Rx product

[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
NDA	21-351	Oxytrol (Oxybutynin Transdermal System)

18. STATUS:

Chemistry Review Data Sheet

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	11/12/2012	Office of Compliance
Pharm/Tox	N/A		
Biopharm	Acceptable	11/12/2012	Dr. T. Ghosh
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Claim for categorical exclusion is granted	10/2/2012	Dr. C. Strasinger
Microbiology	N/A		

The Chemistry Review for NDA 202-211

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 202-211 for Oxytrol for Women is recommended for Complete Response from the CMC perspective. The Applicant has provided sufficient information to assure identity, strength, and purity of the drug product. The Applicant has not provided sufficient information to assure quality based on inadequate acceptance criteria for the presence of (b) (4) A shelf-life of 2 years (24 months) is granted for this product.

Labels and labeling do not have the required information.

An overall "Pending" recommendation has been issued for the manufacturing and testing sites by the Office of Compliance on 23-OCT-2012.

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

No CMC related Phase 4 are proposed at this time.

II. Summary of Chemistry Assessments

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

Drug Substance:

The drug substance, Oxybutynin, is manufactured by (b) (4), and the relevant CMC issues related to the manufacture and quality of this material are described in (b) (4) DMF (b) (4) A satisfactory Letter of Authorization (LOA), dated 8-3-10, was provided to consult this DMF; and the latest up-date of DMF (b) (4) has been found adequate to support this NDA (Oxytrol for Women). Oxybutynin is a racemic mixture, a white (b) (4) powder, and is practically insoluble in water. However the drug substance is freely soluble in ethanol, acetone, methylene chloride, and chloroform. No polymorphism has been reported in the literature for Oxybutynin. The drug substance is accepted based on a Certificate of Analysis from (b) (4) and in-house acceptance testing to show that the Oxybutynin meets its specifications for Appearance, Identification, Melting Temperature, Impurities, Residual Solvents, Loss on Drying, Residue on Ignition, Heavy Metals, Residual Chloride Content and Assay. The applicant also referenced NDA 21351 for the approved drug Oxytrol, and the drug substance specifications are the same as for Oxytrol (Oxybutynin transdermal system). Adequate stability data was provided to support the stability of Oxybutynin in (b) (4)

DMF (b) (4). Accordingly, from a Chemistry, Manufacturing, and Controls (CMC) point of view, the drug substance is deemed acceptable.

Drug Product:
Oxytrol for Women is a transdermal drug delivery system (TDDS) designed to release oxybutynin gradually over a 4 consecutive day period. The system is a three layer matrix design consisting of a translucent backing film, an adhesive matrix and an overlapped-tab release liner that is removed prior to system application. Each system contains 36 mg of oxybutynin in an (b) (4). The only other excipient is triacetin which is used (b) (4). The oxybutynin transdermal system is the same as the approved drug product Oxytrol described in NDA 21-351. The system is designed to deliver approximately 3.9 mg/day. The commercial drug product will be manufactured, packaged and tested by the same facilities as those used for the approved prescription (Rx) product. The manufacturer of the drug product is **Watson Laboratories Inc., Salt Lake City, Utah** while **MSD Consumer Care Inc**. is responsible for the finished drug product secondary packaging and release. Several additional companies have been listed as excipient, microbial, release and stability testing facilities, all of which are domestic.

The quality of the drug product is controlled by tests for appearance, content uniformity, assay, identity, degradation products, triacetin content, drug release, (b) (4), (b) (4) (b) (4), adhesion (b) (4) release liner peel, (b) (4) probe (b) (4) and (b) (4)

The only notable change between the Rx NDA 21-351 and this application is the addition of a child resistant layer to the (b) (4) pouch (immediate container closure). The pouching material is same as described in Oxytrol NDA 21-351 in terms of the product contact materials.

Each pouch will contain one system and will be placed in cartons of the following counts, 4, 10, and 14. The Applicant is requesting (b) (4) of expiration dating however, 24 months is being granted (b) (4).

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

Oxytrol for Women (oxybutynin transdermal system) 3.9 mg/day is a transdermal drug delivery system that releases oxybutynin continuously upon application to intact skin for the treatment of overactive bladder. The adhesive side of Oxytrol for Women should be placed on a clean, dry area of the trunk of the body (including the abdomen, hips or buttocks). The transdermal delivery system is designed for continuous wear with application of a new system after 4 days of wear to a different site with each application. The product should be stored at room temperature.

C. Basis for Approvability or Not-Approval Recommendation

From the ONDQA perspective, this NDA is recommended for Complete Response.

The Labels and Labeling do not contain sufficient information per 21 CFR 314.125 (b) (6).

Office of Compliance has issued a "Pending" overall recommendation for all facilities involved and therefore per 21 CFR 314.125 (b) (13) is not acceptable.

The Applicant has not provided sufficient information to assure quality based on inadequate acceptance criteria for the presence of (b) (4).

The Applicant has provided sufficient information on raw material controls, manufacturing processes and process controls. Sufficient stability information is provided on the drug product in the NDA to assure strength, purity, and quality of the drug product for an expiration dating period of 24 months.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Sheldon Markofsky, PhD; Caroline Strasinger, PhD 31-OCT-2012
ChemistryTeamLeaderName/Date: Swapan De, PhD; 31-OCT-2012
ProjectManagerName/Date: Luz Riveria; 31-OCT-2012

C. CC Block

38 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

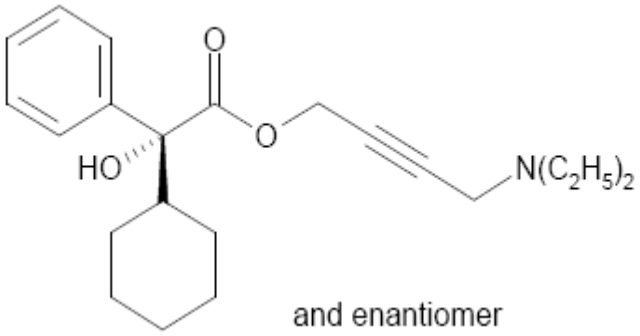
SHELDON B MARKOFSKY
11/16/2012

TERRANCE W OCHELTREE
11/16/2012

Division of Nonprescription Clinical Evaluation

NDA:	**202,211**
Applicant:	MSD Consumer Care, Inc. 555 Morris Avenue Summit, NJ 07901
Stamp Date:	03/26/2012
PDUFA Date:	01/25/2013
Proposed Proprietary Name:	Oxytrol for Women
Established Name:	Oxybutynin transdermal system
Dosage form and strength:	Transdermal; 3.9 mg/day
Route of Administration:	Transdermal
Indications:	Relief of symptoms of over-active bladder in adult women
CMC Lead:	Swapan K De
ONDQA Fileability:	**Yes**

Name: Oxybutynin
Molecular formula: $C_{22}H_{31}NO_3$
Molecular Weight: 357.49



Has all information requested during the IND phases, and at the pre-NDA meetings been included?

Yes

Summary:

This is an e-CTD NDA application for oxybutynin transdermal system (oxybutynin 36 mg patch delivers 3.9 mg/day). The CMC information of this NDA is based on prescription Oxytrol NDA 21-351 commercialized by Watson Pharmaceuticals Inc. The manufacturing operations are same for both NDA regarding manufacturing site (Watson Laboratories Inc.), batch size, raw materials, manufacturing process and equipments with the exception of an additional (b) (4) child resistant pouch stock. Due to the similarity in the CMC information of non prescription Oxytrol to the original prescription Oxytrol NDA 21-351, the submission cross refers or duplicate most of the CMC information from NDA 21-351.

Drug Substance:

Oxybutynin is white (b) (4) powder of racemic mixture and is practically insoluble in water. Drug substance (oxybutynin) information remains unchanged as approved in NDA 21-351. Thus, eCTD sections consisting of general information (3.2.S.1), Manufacture (3.2.S.2), characterization (3.2.S.3), control of drug substance (3.2.S.4), reference standard or material (3.2.S.5), container closure system (3.2.S.6) and stability (3.2.S.7) are mostly duplicated from NDA 21-351. Some additional information includes tightening of specifications for chromatographic purity (assay and melting point) to align with drug substance manufacturer's specifications and addition of a TLC test as a second ID test for the drug substance (to meet ICH Q6A requirements). In addition, new information has been provided for the drug substance batches that are used to manufacture the clinical trial batch and one drug product batch (submitted in the NDA). A letter of authorization has been provided to access the drug substance manufacturer's DMF (b) (4)

Drug Product:

The oxybutynin transdermal system is the same as the drug product described in Oxytrol NDA 21-351. The oxybutynin transdermal system is a three layer matrix design that consists of a translucent backing film, an adhesive matrix, and an overlapped-tab release liner that is removed prior to system application. Individual systems are packed in heat sealed pouches. The translucent backing film is a thin, flexible polyester/ethylene-vinyl acetate (PET/EVA) film that provides the patch with occlusivity and physical integrity and protects the drug/triacetin/adhesive

matrix. The adhesive matrix is a cast film of [redacted] and contains API, oxybutynin base and the [redacted] (triacetin). The third layer is a two overlapped polyester (PET) silicone-coated release linerstrips designed to be peeled off and discarded by the patient prior to applying the patch.

The drug substance and excipients used in the manufacture of oxybutynin transdermal system are identical as approved in NDA 21-351. Formulation development section is updated with justification for residual drug amount in the system after use, based on FDA guidance on "Guidance for Industry, Residual Drug in Transdermal and Related Drug Delivery Systems (Aug 2011)". Manufacturing process for the drug product are similar as approved (NDA 21-351) with the exception of addition of a [redacted] child resistant pouch stock for packaging nonprescription Oxytrol.

The container closure system (pouch) of the OTC drug product (NDA 202, 211) will have a change from the approved NDA (NDA 21,351). The prescription drug product is packaged in a peelable pouch, which consists of several layers and they are [redacted] respectively from inside (product-contact) to outside. The [redacted] layer of the prescription Oxytrol pouching material has been changed to a PET layer to [redacted].

In vitro drug release profile comparison has been provided to demonstrate that the change in manufacturing equipments have no impact on the bioavailability of the drug product. It is stated that prior to commercialization, three validation batches will be manufactured using [redacted]. The specifications of the drug products remain same as approved in NDA 21-351 except degradation products and [redacted]. Justification for the changes in degradation products and [redacted] is included. Oxytrol drug product release and stability specifications comparison has been provided and shown below.

Oxytrol Drug Product Release Specification Comparison:

Test	Prescription Oxytrol Release Specification	Nonprescription Oxytrol Release Specification
Appearance	System, translucent, packaged in a heat sealed pouch	System, translucent, packaged in a heat sealed pouch
Content Uniformity	Conforms to current USP <905>	Conforms to current USP <905>
Identity: Oxybutynin (HPLC)	Matches retention time of reference standard	Matches retention time of reference standard
Identity: Area Dimensions Width Length	 5.4 – 5.9 cm 7.3 – 7.8 cm	 5.4 – 5.9 cm 7.3 – 7.8 cm
Oxybutynin Assay	(b) (4) Label Claim	(b) (4) Label Claim
Degradation Products (b) (4) Unknown, Individual (area basis) Unknown, Total (area basis)	 NMT (b) (4) NMT NMT NMT NMT NMT	 NMT (b) (4) NMT NMT NMT NMT NMT
Triacetin Content	(b) (4) mg/system	(b) (4) mg/system
Drug Release 1 Hours 4 Hours 24 Hours	Conforms to USP <724> (b) (4) Label Claim Label Claim (b) (4) Label Claim	Conforms to USP <724> (b) (4) Label Claim Label Claim (b) (4) Label Claim
(b) (4)	NMT (b) (4) NMT	NMT (b) (4) NMT NMT NMT (b) (4)
Adhesion to (b) (4)	NLT (b) (4)	NLT (b) (4)
Release Liner Peel*	Functional (Action Limit NMT (b) (4) g/in)	Functional (Action Limit NMT (b) (4) g/in)

* Release Liner Peel Force specification is proposed as "functional", where functional is defined as the release liner is adhered to 100% of the system area and removal of the release liner does not result in damage to the adhesive. Systems with the average release liner peel force results outside the action limit will be investigated.

(b) (4)

NMT :Not More Than; NLT : Not Less Than

Oxytrol Drug Product Stability Specification Comparison:

Test	Prescription Oxytrol Stability Specification	Nonprescription Oxytrol Stability Specification
Appearance	System, translucent, packaged in a heat sealed pouch	System, translucent, packaged in a heat sealed pouch
Oxybutynin Assay	(b) (4) Label Claim	(b) (4) Label Claim
Degradation Products (b) (4) Unknown, Individual (area basis) Unknown, Total (area basis)	 NMT (b) (4) NMT NMT NMT NMT NMT	 NMT (b) (4) NMT NMT NMT NMT NMT
Triacetin Content	(b) (4) mg/system	(b) (4) mg/system
Drug Release 1 Hours 4 Hours 24 Hours	Conforms to USP <724> (b) (4) Label Claim Label Claim (b) (4) Label Claim	Conforms to USP <724> (b) (4) Label Claim Label Claim (b) (4) Label Claim
Adhesion to (b) (4)	NLT (b) (4)	NLT (b) (4)
Release Liner Peel*	Functional (Action Limit NMT (b) (4) g/in)	Functional (Action Limit NMT (b) (4) g/in)

* Release Liner Peel Force specification is proposed as "functional", where functional is defined as ' the release liner is adhered to 100% of the system area and removal of the release liner does not result in damage to the adhesive. Systems with the average release liner peel force results outside the action limit will be investigated

(b) (4)

NMT :Not More Than; NLT : Not Less Than

Drug product release testing results for the submission batch of OTC Oxytrol oxybutynin systems (Batch #424540, Drug substance Lot# 0004287196) has been provided. Stability data for the same submission batch has been provided up to 3 months at both long term conditions (25°C/60% RH) and accelerated conditions (40°C/75% RH). The applicant has proposed (b) (4) shelf-life of the nonprescription Oxytrol (b) (4)

Critical Issues:

Drug substance:

- DMF (b) (4) should remain adequate to support the NDA 202-211. It should contain manufacturing process details with appropriate critical process parameters, specifications with impurity profile for the drug substance and stability data to support a retest period.

Drug Product:

- There is detailed formulation development section in 3.2P which should be evaluated in-depth.

- Is the limit for degradation product specifically for [redacted] (b) (4)) deemed justified and reasonable?
- Has adequate justification been provided for not including the microbial limits test in the release specification of nonprescription Oxytrol? Microbiological Attributes section 3.2.P.2.5 is included and needs a consult review by a microbiologist.
- In vitro dissolution comparison among the prescription Oxytrol (NDA 21-351) and nonprescription Oxytrol should be consulted to the Biopharmaceutics team in ONDQA. They should also review the updated dissolution method in section 3.2P. This method has been updated also for NDA 21-351 (Annual report dated 04/09/2011).
- The analytical procedures of the drug product for Assay/Content Uniformity, Degradation Products, [redacted] (b) (4) and Triacetin has been updated for NDA 21-351 (Annual report dated 04/09/2011) as well as for this NDA (#202-211). Are these method appropriately validated?
- Is the submitted 3-month stability data for one batch of drug product is enough to support the proposed [redacted] (b) (4) shelf-life of the nonprescription Oxytrol with altered container closure system which is different from the approved prescription Oxytrol product?

Comments and Recommendations:

The application is fileable. The CMC information remains very similar as approved in NDA 21-351. Submitted manufacturing facilities have been entered into the EES. The reviewer should confirm the accuracy and completeness of the EES entries. This NDA does not qualify as a QbD submission based on the criteria in the ONDQA interim policy (no design space, PAT, RTRT, reduced end-product testing etc.).

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: #202,211

Established/Proper Name: Oxybutynin Transdermal System 3.9 mg/day/Oxytrol for Women

Applicant: MSD Consumer Care

Letter Date: 03/26/2012

Stamp Date: 03/26/2012

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		Looks to be in standard eCTD format.
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		Appears to be
3.	Are all the pages in the CMC section legible?	X		Appears to be
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		Appears 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		Nine facilities identified, all have complete addresses and FEI Numbers.
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		Appears to be
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		Appears to be

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		Appears to be.
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* 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		Appears to be

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	Refers to (b) (4) DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	Refers to (b) (4) DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?		X	Refers to (b) (4) DMF (b) (4)
15.	Does the section contain controls for the DS?		X	Refers to (b) (4) DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?		X	Refers to (b) (4) DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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		Appears to be
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		Appears to be
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Pharmaceutical development section has adequate information.
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		Appears to be
25.	Does the section contain controls of the final drug product?			Appears to be
26.	Has stability data and analysis been provided to support the requested expiration date?			Limited data has been included and needs to be evaluated
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?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?		X	Needs to be requested based on reviewers judgment.

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		Microbiological Attributes section 3.2.P.2.5 is included and needs to be reviewed by a microbiologist.

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		Appears to be

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		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
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.		X	
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		It would depend on initial review by the reviewer.

{See appended electronic signature page}

Swapan K De
CMC Lead
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

{See appended electronic signature page}

Ali Al Hakim
Branch Chief
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

Manufacturer(s) of Oxybutynin Transdermal System

Drug Substance (Oxybutynin Base) Manufacturer:

Manufacturing Site	Responsibilities
(b) (4)	Drug substance manufacture In-process control and testing Drug substance testing Drug substance packaging Stability testing
Watson Laboratories, Inc. 577 Chipeta Way Salt Lake City, UT Establishment #1000117147 A listing of contract laboratories used by Watson for compendial testing is provided in 3.2.P.3.1.	Drug substance testing Final release control for use in the drug product.

Drug Product (Oxybutynin Transdermal System) Manufacturer:

Name and Address	Responsibility/Function
Watson Laboratories, Inc. 575 & 577 Chipeta Way Salt Lake City, UT Establishment #1000117147	Drug product manufacture. Drug product packaging. Release testing of drug substance and excipients. In-process testing. Release testing of packaging materials. Drug product testing and release. Drug product stability testing.

Table 2. Secondary Packaging Sites

Name and Address	Responsibility/Function
MSD Consumer Care Inc. 4207 Michigan Avenue Road Cleveland, TN 37323 Establishment # 1031623	Secondary packaging of the drug product. Release of the drug product.
(b) (4)	Alternate site for secondary packaging of the drug product.

Contract Analytical Laboratory	Responsibility
(b) (4)	Contract laboratory for compendial testing of raw materials and container/closure systems. Laboratory for microbial testing of finished products.
	Contract laboratory for compendial testing of raw materials and container/closure systems.
	Laboratory for microbial testing of finished products.
	Contract laboratory for compendial testing of drug substance, excipients, and container/closure systems. Laboratory for microbial testing of finished products.

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

/s/

SWAPAN K DE
05/02/2012

ALI H AL HAKIM
05/02/2012