ONDQA (Biopharmaceutics) Review

NDA	202- 211 (000)
Applicant:	MSD Consumer Care, Inc.
Trademark:	Oxytrol for Women
Stamp Date	March 26, 2012
Established Name:	Oxybutynin Transdermal System
Dosage Form:	Transdermal; 3.9 mg/day
Route of Administration:	Topical
Indication:	Relief of symptoms of over-active bladder in adult women
Reviewer	Tapash Ghosh, Ph.D.

OVERALL ASSESSMENT:
As there is no change in formulation and the Applicant has appropriately bridged the batches manufactured by slightly modified equipments, the Applicant's proposal to use the approved *in-vitro* drug release acceptance criteria using the previously approved and validated analytical methodologies is acceptable.

RECOMMENDATION
From the Biopharmaceutics view point NDA 202- 211 (000) for Oxytrol for Women (Oxybutynin transdermal system 3.9 mg/day) is recommended for approval.

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer
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BIOPHARMACEUTICS ASSESSMENT

Summary:

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

This Biopharmaceutics review evaluates only the proposed *in-vitro* drug release method and acceptance criteria. The *in vitro* drug release profile comparison and f2 data demonstrate that the changes in the manufacturing equipments have no impact on the bioavailability of the drug product.

Proposed *In-vitro* Drug Release Method and Acceptance Criteria:

The *in-vitro* drug release methodology and acceptance criteria proposed for non-prescription Oxytrol for Women remain the same as those approved for the original prescription Oxytrol under NDA 21-351 as shown below:

Drug Release Method :

Equipment: USP Paddle Over Disk – USP Apparatus 5

3.1	Dissolution System Operating Conditions	
	PADDLE POSITION:	25 ± 2 mm above the TDS surface
	VESSEL TEMPERATURE:	32 ± 0.5°C
	PADDLE SPEED:	50 ± 1 rpm
	DISSOLUTION SOLUTION:	900 mL

Analytical Method:

3.2.P.5.2.8.5.3 HPLC Analysis Method

HPLC Conditions

COLUMN:	Agilent Xorbax Bonus-RP (3.5 µm, 4.6 mm x 75 mm) with MacMod Column Saver pre-column filter
COLUMN TEMPERATURE:	30°C
MOBILE PHASE:	ACN: 10mM phosphate buffer pH 8.0 isocratic (60: 40, v/v)
MOBILE PHASE FLOW RATE:	1.4 mL/min
SAMPLE INJECTION VOLUME:	50 microliters
DETECTOR WAVELENGTH:	240 nanometers
RUN TIME:	Adequate runtime is approximately 4 minutes

Proposed Drug Release Criteria:

Level	Number Tested	Criteria
L1	6	No individual values lie outside the stated range
L2	6	The average value of the 12 units (L1+L2) lies within the stated range. No individual value is outside stated range by more than 10% of the average of the stated range.
L3	12	The average value of the 24 units (L1+L2+L3) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average for the stated range; and none of the units is outside the stated range by more than 20% of the average of the stated range.

Test Method	TM-1006	
Test	Release Specification	Shelf-Life Specification
Drug Release	Conforms to USP <724>	Conforms to USP <724>
1 Hours	(b) (4) Label Claim	(b) (4) Label Claim
4 Hours	Label Claim	Label Claim
24 Hours	Label Claim	(b) (4) Label Claim

Reviewer's Comment:

The Applicant's proposal to use the approved in-vitro drug release acceptance criteria using the previously approved and validated analytical methodologies is acceptable.

***In-Vitro* Dissolution Comparison to support Manufacturing Equipment Change**

In order to demonstrate that the change in manufacturing equipment will have no impact on the bioavailability of the drug product, an *in-vitro* drug release profile comparison

study was performed. The drug release of a batch produced using currently approved (b) (4) was compared to a batch produced using (b) (4) An f2 value between 50 and 100 demonstrates that two dissolution profiles are similar. The *in vitro* dissolution profile comparison yielded an f2 value of 74.8. Therefore, the drug release profiles are considered similar (see below).

f2 Comparsion between Oxtyrol Transdermal System, 3.9 mg/day produced on (b) (4) versus validated (b) (4)

Product 1: 52544092008
Lot: 273577
Report Date: 02-Jun-10
Lot Description: Batch Manufactured on (b) (4) using (b) (4) Triacetin for (b) (4) (b) Material Qualification Protocol (4)

Product 2: R900411
Lot: 424540
Report Date: 05-Jul-11
Lot Description: Batch manufactured on (b) (4) using (b) (4) Triacetin for (b) (4) Demonstration Batch Execution

	Drug Release Time (h) Average %LC n=18		
Equipment	1	4	24
(b) (4)			

(b) (4)

CALCULATION OF SUPAC f2 VALUE

(b) (4)

Reviewer's Comment:
The dissolution profile comparison and f2 data support the approval of the proposed manufacturing equipment changes.

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/s/

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11/16/2012

ANGELICA DORANTES
11/16/2012