ONDQA (Biopharmaceutics) Review

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

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
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment
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][c] 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: 10 mM 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:**

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>6</td>
<td>No individual values lie outside the stated range</td>
</tr>
<tr>
<td>L2</td>
<td>6</td>
<td>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.</td>
</tr>
<tr>
<td>L3</td>
<td>12</td>
<td>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.</td>
</tr>
</tbody>
</table>

**Test Method**

<table>
<thead>
<tr>
<th>Test</th>
<th>Release Specification</th>
<th>Shelf-Life Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Release 1 Hours</td>
<td>Conforms to USP &lt;724&gt; Label Claim</td>
<td>Conforms to USP &lt;724&gt; Label Claim</td>
</tr>
<tr>
<td>4 Hours</td>
<td>Label Claim</td>
<td>Label Claim</td>
</tr>
<tr>
<td>24 Hours</td>
<td>Label Claim</td>
<td>Label Claim</td>
</tr>
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**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 materials was compared to a batch produced using.

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).

**Reviewer’s Comment:**
The dissolution profile comparison and f2 data support the approval of the proposed manufacturing equipment changes.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAPASH K GHOSH
11/16/2012

ANGELICA DORANTES
11/16/2012