

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202211s000**

**OTHER REVIEW(S)**

# Labeling Review for Oxytrol for Women (Oxybutynin) Transdermal System

---

---

**SUBMISSION DATES:** December 7, 2012  
January 15, 2013  
January 22, 2013

**RELATED SUBMISSIONS** March 26, 2012  
June 25, 2012  
September 04, 2012

**NDA/SUBMISSION TYPE:** 202-211

**ACTIVE INGREDIENTS:** Oxybutynin 3.9 mg/day

**DOSAGE FORM** Transdermal System

**SPONSOR:** MSD Consumer Care, Inc.  
MSD Morris Avenue  
Summit, NJ 07901  
Authorized Agent:  
Nancy Pierro, Associate Director, Regulatory Affairs  
908-474-5709  
Fax: (908) 473- 3814

**REVIEWER:** Maria Ysern, IDS, DNRD, ODE IV

**TEAM LEADER:** Ruth E Scroggs, PharmD, DNRD, ODE IV

**REGULATORY PROJECT  
MANAGER** Melissa H. Furness, Chief Project Manager, DNCE, ODE IV

---

---

## I. BACKGROUND

Merck Consumer Care, Inc. (MCC) submitted March 26, 2012, an original NDA under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act to change the marketing status of Oxytrol (oxybutynin) Transdermal System, NDA 21-351, from Rx to over-the-counter (OTC). The proposed switch is for the target population of women, 18 years of age and older, for use in the treatment of overactive bladder. The use of Oxytrol by males will remain a prescription indication.

Labeling amendments dated December 7, 2012, January 15, and January 22, 2013 were submitted. This review, the second of two, amends our November 27, 2012 labeling review. This is a review of labeling submitted via email to the Agency on January 22, 2013 compared to the labeling reviewed November 27, 2012.

Submitted Labeling	Representative of the Following SKUs	Submission date/replaces
1-count Immediate Container	The same one-count pouch will be used for each package size.	January 15, 2013 replaces March 26, 2012
4-count Carton	2-, 8-, 14-count	January 22, 2013 replaces January 15, 2013
10-count Carton (25 % more free (2 free patches))	none	January 22, 2013 replaces January 15, 2013
14-count Club Store Backer Card	none	January 22, 2013 replaces March 26, 2012
14-count Club Store Backer Card (showing carton principal display panel)	none	January 22, 2013 replaces March 26, 2012
Consumer Information Leaflet (CIL)	The same CIL will be used for each package size.	January 22, 2013 replaces January 15, 2013

## II. REVIEWER'S COMMENTS

### A. 4- (representative of 2-, 8-, and 14-count ) and 10-count cartons

#### i. Outer Carton Label Outside Drug Facts

- a. For the 4- count cartons, the PDP's top left corner shows a yellow flag with the following letters in blue: "New !".  
**Comment: This is acceptable. Please remind the sponsor to delete the yellow flag after six months of marketing,**
- b. For the 10-count carton (8 plus 2 free), there is a yellow banner across the top of the PDP, with the statement in blue letters "25% More Free". On the right side of the banner the sponsor has specified in parenthesis (2 free patches).  
**Comment: This responds to our January 10, 2013 labeling comments. In accordance with Section 502(a) of the Federal Food, Drug, and Cosmetic Act (FD & C Act), the sponsor revised the carton label to clearly communicate to consumers**

**the quantity of extra free transdermal systems available. It indicates there are two more patches (transdermal systems) per package. It is therefore acceptable.**

- c. On the PDP, top flap, and left and right panels, the silhouette of a woman, located on the left side of the proprietary name of the product is revised to show a woman with a thin waist and slightly leaning back.

**Comment: This is acceptable.**

- d. The prominence of the both the designated dosage form and strength expressed as daily dosage (rate) is revised by using heavier darker font. The daily dosage is reformatted from 3.9MG/DAY to read 3.9 mg/day so that there is space between the letter 9 and the letter m and the letters are in lower case.

**Comment: This responds to our January 10, 2013 labeling comments. This is acceptable.**

- e. The stated designated dosage form located within the statement of net quantity is revised so that the words “transdermal system” within parentheses are inserted below the word “patches”.

**Comment: The Agency’s January 10, 2013 labeling comments requested that the designated dosage form be revised from (b) (4) to “transdermal system”. In MCC’s submission of January 15, 2013, an alternative option was proposed as “patch (transdermal system)”. They state that all of the studies conducted in support of this application had labeling with the designated dosage form described as “patch”. This proposed revision was discussed at the January 18, 2013 internal labeling meeting and found acceptable.**

- f. The country of origin statement, “Product of Switzerland” located on the back panel, below Drug Facts is deleted.

**Comment: This is acceptable. In the January 22, 2013 submission, the firm states that after reviewing the regulations at 19 CFR 102 and Custom ruling HQ 562316 (April 1, 2002) they have determined that the active pharmaceutical ingredient undergoes a substantial transformation within USA as it is manufactured into the transdermal system.**

- g. The carton PDP has a different shade of pink.

**Comment: This is acceptable.**

## **ii. Outer Carton Drug Facts Label**

### **a. Active ingredient/Purpose**

1. The heading is revised from “Active ingredient (in each patch)” to “Active ingredient (in each patch [transdermal system])”.

**Comment: The January 15, 2013 submission responded to our January 10, 2013 labeling comments requesting that the Active ingredient statement be updated to include “(transdermal system)”. The firm proposed square brackets, instead of two close-parenthesis side-by-side. This was found acceptable during a January 18, 2013 internal labeling meeting.**

2. Below the heading, the dosage form (b) (4) is deleted so that the line is revised from “Oxybutynin transdermal system 3.9 mg/day to “Oxybutynin 3.9 mg/day”.  
**Comment: The January 10, 2013 submission addresses our December 20, 2012 labeling comments. Transdermal system is not part of the active ingredient under 21 CFR 201.66(c)(2), therefore this is acceptable.**
  3. The first letter of “overactive” in the purpose statement is revised to uppercase “O”.  
**Comment: This addresses our December 20, 2012 labeling comments. This is acceptable as required under 21 CFR 201.66(d)(1).**
- b. *Use*
1. The second bullet is revised so that the last three words are bolded to appear as [bullet] you may be suffering from overactive bladder if you have had 2 or more of the following symptoms for at **least 3 months:**”  
**Comment: This revision was requested in our December 20, 2012 labeling comments. Therefore, this is acceptable.**
  2. A new statement is added as a third bullet. It reads: “[bullet] non-drug therapies may also help you (see consumer information leaflet inside the package)”  
**Comment: Our December 20, 2012 labeling comments requested the new statement. Therefore, this is acceptable.**
- c. *Warnings*
1. A new bolded warning “**For external use only** “ is inserted directly under the “Warnings” heading.  
**Comment: This responds to our December 20, 2012 labeling comments. The patch is a topical product, not intended for ingestion; therefore the “For external use only” warning is required under 21 CFR 201.66(c)(5)(i). This is acceptable.**
  2. The third warning statement “**If you think you might have one of these conditions, see your doctor before use.**” is revised by insertion of “it is important to” to read as: “**If you think you might have one of these conditions, it is important to see your doctor before use.**”  
**Comment: This addresses our December 20, 2012 labeling comments. Therefore, it is acceptable.**
  3. A new fourth bolded warning is inserted; “**Sleepiness, dizziness, and blurry vision may occur. Do not drive or operate machinery until you know how the patch affects you.**”  
**Comment: This warning about potential side effects that may occur and activities to avoid while using the drug product was requested in our December 20, 2012 labeling comments. The first sentence is similar to the one deleted from the “When using this product” section. Under 21 CFR 201.66(e), FDA on its**

own initiative, or at the request of the sponsor, may exempt certain labeling requirements. Therefore, this is acceptable.

**Subsection: Do not use if you**

4. The second bullet “are male” is now followed by the added following information: “Your symptoms may be due to a more serious condition.” to read: “[bullet] are male. Your symptoms may be due to a more serious condition.”

**Comment: This revised contraindications warning was requested in our December 20, 2012 labeling comments. It is therefore acceptable.**

5. The third bullet is modified by adding “It is not known if it works or is safe in children.” to read as “[bullet] are under the age of 18. It is not known if it works or is safe in children.”

**Comment: This revision of the pediatric contraindication warning responds to our December 20, 2012 labeling comments. It is therefore acceptable.**

6. The seventh bullet is revised from “have narrow-angle glaucoma” to read “[bullet] have glaucoma” by deleting “narrow-angle”.

**Comment: This responds to our December 20, 2012 labeling comments. It is therefore acceptable.**

**Subsection: Ask a doctor before use if you have**

7. The first bullet “risk factors or symptoms of diabetes, such as:” is revised by deleting “risk factors” to read as [bullet] symptoms of diabetes, such as:”
8. The first sub bullet “a history of diabetes in your immediate family” was deleted, leaving “excessive thirst” as the sub bullet.
9. The fourth sub bullet “increased tiredness” is deleted.
10. The third bullet “a history of kidney stones” is deleted.

**Comment: The changes made in no. 7 to no. 10 respond to our December 20, 2012 labeling comments. Therefore, they are acceptable.**

**Subsection: Ask a doctor or pharmacist if you are**

11. The second bullet is revised by deleting “diuretic (commonly called water pills) and adding new language to read [bullet] taking any drugs that may cause sleepiness, dizziness, dry mouth, constipation or blurred vision”

**Comment: This revised language was discussed at our January 18, 2013 internal labeling meeting and responds to our January 18, 2013 labeling comments. It is therefore acceptable.**

12. A third bullet is added “[bullet] taking certain antibiotics (for example, erythromycin, clarithromycin) or prescription antifungals (for example, ketoconazole, itraconazole)”

**Comment: This responds to our December 20, 2012 labeling comments. Therefore, it is acceptable.**

**Subsection: When using this product**

13. The first bullet “you may see mild irritation when the patch is removed, this usually goes away in several hours” is replaced by “[bullet] you may have itching, rash or redness where the patch was placed”

**Comment: This is acceptable. The Agency recommended this December 20, 2012.**

14. The second bullet “sleepiness, dizziness or blurred vision may occur” is deleted from this section and moved to the main Warnings section to become the first sentence of the third Warnings statement. Subsequently, the third bullet “drinking alcohol may increase sleepiness” becomes the second bullet.

**Comment: These are acceptable changes as recommended by the Agency December 20, 2012.**

15. The fourth bullet “use caution when driving a motor vehicle or operating machinery” is deleted from this section.

**Comment: This is acceptable. A revised version “Do not drive or operate machinery until you know how the patch affects you.” is a new warning under the main Warnings heading.**

**d. Directions**

1. The first sentence within the first bullet under “How to use the patch:” was modified by replacing “open individual pouch and apply immediately to a clean, dry and smooth area of skin on...” with “open 1 pouch and apply patch immediately to a clean, dry and smooth area of skin...”

**Comment: This is acceptable.**

2. A new 8<sup>th</sup> bullet is added “[bullet] if a patch falls off and you cannot press it back onto your skin, use a new patch”

**Comment: The statement is acceptable**

**e. Inactive ingredients**

Inactive ingredients are revised to read: “acrylic adhesive and triacetin delivered on a polyester/ethylene-vinyl acetate film”

**Comment: Under 201.66, Inactive ingredient means any component other than an active ingredient and must be listed in alphabetical order. The sponsor has corrected this section. Therefore, this is acceptable.**

**f. Questions or comments?**

The Questions or comments? section has been modified by inserting an alpha-numeric toll free telephone number “1-888-OXYTROL” before/adjacent to the all numeric toll free telephone number to read as “Call toll free: 1-888-OXYTROL ( 1888-699-8765) between 8:00 AM and 5:00 PM Central Standard Time, Monday through Friday”

**Comment: This change is acceptable.**

**g. Other Sections/Issues**

Format Specifications

The labeling legend indicates that the square bullets are 4.5 point Zaph Dingbats no compression.

**Comment: Although 5 point solid square bullets are *strongly* recommended by FDA, the 4.5 point Zaph Dingbats font square bullets are of similar if not identical size. They serve their intended purpose in clearly delineating the Drug Facts labeling. Therefore, they are acceptable.**

**B. 14-count Club Store Pack Backer Card**

**i. Label Outside the Drug Facts**

- a. This labeling component is a card printed so that the Drug Facts appears on the back and the PDP appears on the front side. The front part of the card has window, through which the principal display panel of the 14-count carton label will appear. The back of this card contains the Drug Facts label and other non-Drug Facts information.

**Comment: Recommendations for the Club Pack are consistent with recommendations made under II.A.i.a to g. Therefore, this is acceptable.**

The back panel below the Drug Facts has been modified to delete “Product of Switzerland.

**Comment: This is acceptable.**

**ii. Label Outside Drug Facts:**

The Drug Facts content on each carton are identical. Refer to section II.A. ii.

**iii. Immediate Container (1-count Pouch) Label**

- a. Front panel – Changes made to the one count pouch, match the carton PDP (different shade of pink, changes to silhouette graphic). The firm incorporated our proposals on the immediate container, with the exception of the location of the statement of identity and the designated dosage form.

**Comment: These are acceptable changes. See section I.A.i.**

- b. Back panel- In the upper left corner, “For external use only” is inserted below the word “Warnings”

**Comment: This revision submitted January 15, 2013 was made in response to our January 10, 2012 labeling comments. Therefore, it is acceptable.**

- c. The pre-existing conditions yellow highlighted warning is revised consistent with Drug Facts.

**Comment: This is acceptable. See section I.A.ii.**

- d. The  <sup>(b) (4)</sup> statement below the yellow highlight has been deleted.

**Comment: Drug Facts on the cartons lists this warning and is not required on the pouch. Therefore, this is acceptable.**

- e. The Directions and Questions or Comments sections are consistent with Drug Facts sections on the cartons.

**Comment: This is acceptable. See section I.A.ii.**

**“Product of Switzerland” is deleted from the lower left corner.”**

**Comment: This is consistent with the carton labeling/sponsor’s justification and therefore acceptable. See section I.A.i.**

#### **iv. Consumer Information Leaflet**

The Consumer Information Leaflet (CIL) is entitled “Oxytrol for Women Tips to Help Manage Your Overactive Bladder”. The content has three main sections, each with bulleted lists describing the lifestyle changes consumers can try: “1. Be Aware of what you Eat and Drink and Your Bathroom Habits, 2. Tips to help Retrain Your Bladder, and 3. Lifestyle Changes You Can Make”. It has made all the revisions suggested by the Agency. The template has been updated to reflect what will be used in commercial production and includes a fold area within the words “Consumer Information Leaflet” and Oxytrol for Women”. The woman silhouette graphic has been updated to match other labeling components.

**Comment: The first consumer information leaflet (CIL) was submitted by MCC the Agency on December 7, 2013, amended January 15, 2013 and January 22, 2013 in response to Agency labeling comments. Although the statement about keeping the CIL sent to the firm in January 18, 2013 labeling comments is not incorporated into the January 22, 2013 CIL; from an IDS perspective, the CIL submitted January 22, 2013 is acceptable.**

### **III. RECOMMENDATIONS:**

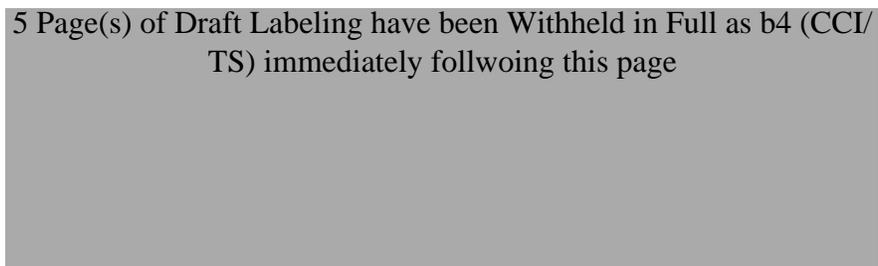
Issue an **APPROVAL** letter to the sponsor for the submitted Oxytrol for Women (oxybutynin) 3.9 mg/day labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: 1-count immediate container (pouch) dated January 15, 2013 4-count carton (representative of the 2-, 8-, and 14-count cartons), 10-count carton, 14-count Club Store Backer Card, and the Consumer Information Leaflet dated January 22, 2013, and must be in the “Drug Facts” format (21 CFR 201.66), where applicable.

The sponsor’s submission dated January 22, 2013, notified us that the 4-count carton is intended to serve as a representative package size for the 2-, 8-, and 14-count cartons. Any changes approved for the 4-count label(s) will be incorporated onto the labels of the other 2-, 8-, and 14-count package sizes, which are identical to the 4-count label(s) with the exception of the count size.

**IV. SUBMITTED LABELING**

The labels on the remaining pages of this labeling review were submitted and were evaluated in this labeling review:

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



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

/s/  
-----

MARIA E YSERN  
01/24/2013

RUTH E SCROGGS  
01/24/2013



NDA 202211

**LABELING COMMENTS**

Merck Consumer Care  
Attention: Nancy Pierro  
Director, Regulatory Affairs  
556 Morris Avenue  
Summit, NJ 07901

Dear Ms. Pierro:

Please refer to your March 26, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxytrol for Women (oxybutynin) transdermal system, 3.9 mg.

We also refer to our June 4, 2012, letter in which we notified you of our target date of December 17, 2012 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On March 26 and December 10, 2012, and January 16, 2013 we received your proposed labeling as part of your submission of this application. We propose labeling revisions to the consumer information leaflet (CIL) and the "Drug Facts" label (DFL) as follows:

- Drug Facts Label - We have carefully considered and agree with your rationale for not adding "you may have dry mouth or constipation" to the "When using this product" section of the Drug Facts Label. After reviewing the data and the prescription labeling for Oxytrol, we recommend that you add "constipation" to the list of symptoms in the phrase "taking any drugs that may cause sleepiness, dizziness, dry mouth or blurred vision" that appears in the "Ask a doctor or pharmacist before use if you are" section.
- Consumer Information Leaflet - We recommend that you add "Important – Please Read" along the top of the Consumer Information Leaflet.

Please note that these revisions have been reviewed and cleared to the level of Cross-Discipline Team Leader.

If you have any questions, please call Melissa Furness, Chief of the Project Management Staff, at (301) 796-0893.

Sincerely,

*{See appended electronic signature page}*

Lesley-Anne Furlong, M.D., M.S.  
Cross-Discipline Team Leader  
Division of Nonprescription Clinical Evaluation  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

ENCLOSURES:

“Drug Facts” Label  
Consumer Information Leaflet

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

/s/  
-----

LESLEYANNE FURLONG  
01/18/2013



NDA 202211

**LABELING COMMENTS**

Merck Consumer Care  
Attention: Nancy Pierro  
Associate Director, Regulatory Affairs  
556 Morris Avenue  
Summit, NJ 07901

Dear Ms. Pierro:

Please refer to your March 26, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxytrol for Women (oxybutynin) transdermal system, 3.9 mg.

We also refer to our June 4, 2012, letter in which we notified you of our target date of December 17, 2012 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.”

On March 26 and December 10, 2012, we received your proposed labeling as part of your submission of this application. We have enclosed proposed labeling revisions to the immediate container (pouch), principal display panel (PDP) of the carton label, the consumer information leaflet (CIL), and the annotated version of the “Drug Facts” label (DFL) that we sent to you on December 20, 2012. Please note that these revisions have been reviewed and cleared to the level of Cross-Discipline Team Leader.

Lastly, we have the following responses to the requests for clarification that you sent to the Agency inquiring as to why we recommend the following changes in the “When using this product” subheading of DFL in our December 20, 2012 communication to you:

- The addition of the text “you may have dry mouth and constipation”
- The removal of the text: “you may see mild redness when the patch is removed, this usually goes away in several hours.”

The review team felt that dry mouth and constipation are significant problems, particularly for the elderly, and appear to be among the reasons why people discontinue the product. It therefore seems important to provide the information. Constipation is also an issue for oxybutynin noted in the Beers criteria.

While we agree with various types of skin irritation being far and away the most common adverse events reported in the clinical trials, we felt that removing this nonserious and likely obvious-to-the-consumer reaction would open up some space on DFL for other messaging. We note that severe redness, itching, or blistering already appears under “Stop use and ask a doctor.” Additionally, your proposed text seemed to us to overstep Rx labeling. Something like “you may have itching, rash or redness where the patch was placed” would be more consistent with Rx labeling.

If you have any questions, please call Melissa Furness, Chief of the Project Management Staff, at (301) 796-0893.

Sincerely,

*{See appended electronic signature page}*

Lesley-Anne Furlong, M.D., M.S.  
Cross-Discipline Team Leader  
Division of Nonprescription Clinical Evaluation  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

ENCLOSURES:

“Drug Facts” Label  
Consumer Information Leaflet  
Comments on the Immediate Container and PDP

4 Page(s) of Draft Labeling have been  
Withheld in Full as b4 (CCI/TS) immediately  
following this page

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

/s/  
-----

LESLEYANNE FURLONG  
01/10/2013



NDA 202211

**LABELING COMMENTS**

Merck Consumer Care  
Attention: Nancy Pierro  
Associate Director, Regulatory Affairs  
556 Morris Avenue  
Summit, NJ 07901

Dear Ms. Pierro:

Please refer to your March 26, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxytrol for Women (oxybutynin) transdermal system, 3.9 mg.

We also refer to our June 4, 2012, letter in which we notified you of our target date of December 17, 2012 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On March 26, 2012, we received your proposed labeling as part of your submission of this application, and have proposed revisions to the "Drug Facts" label that are included as an enclosure. These revisions have been reviewed and cleared to the level of Cross-Discipline Team Leader.

If you have any questions, call me at (301) 796-0893.

Sincerely,

*{See appended electronic signature page}*

Melissa Hancock Furness  
Chief, Project Management Staff  
Division of Nonprescription Clinical Evaluation  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

ENCLOSURE:

"Drug Facts" Label

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

MELISSA H FURNESS  
12/20/2012

# Labeling Review for Oxytrol for Women (Oxybutynin) Transdermal System *Draft Labeling*

---

**SUBMISSION DATES:** March 26, 2012  
June 25, 2012  
September 04, 2012

**NDA/SUBMISSION TYPE:** 202-211

**ACTIVE INGREDIENTS:** Oxybutynin. 3.9 mg/day

**DOSAGE FORM** Transdermal System

**SPONSOR:** MSD Consumer Care, Inc.  
MSD Morris Avenue  
Summit, NJ 07901  
Authorized Agent:  
Nancy Pierro, Associate Director, Regulatory Affairs  
908-474-5709  
Fax: (908) 473- 3814

**REVIEWER:** Maria Ysern, IDS, DNRD, ODE IV

**TEAM LEADER:** Ruth E Scroggs, PharmD, DNRD, ODE IV

**REGULATORY PROJECT  
MANAGER** Melissa H. Furness, Chief Project Manager, DNCE, ODE IV

---

## I. BACKGROUND

Merck Consumer Care, Inc. submitted March 26, 2012 an original NDA under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act to change the marketing status of Oxytrol (oxybutynin) Transdermal System, NDA 21-351, from Rx to over-the-counter (OTC) The proposed switch is for the target population of women, aged 18 and over, for use in the relief of overactive bladder. The use of Oxytrol by males will remain a prescription indication. On April 1, 2011, Schering-Plough Health Care Products, Inc. changed its legal entity name to MSD Consumer Care Inc., operating under the trade name Merck Consumer Care (MCC).

Watson Pharmaceuticals, Inc., the holder of NDA 21-351 for the Rx Oxytrol transdermal system, has granted MCC the right of reference to the data in their NDA. The firm claims three years of exclusivity, as the actual use study conducted in support of this program meets the definition of a “new clinical investigation”.

The following labeling was submitted on March 26, 2012 for review and amended September 04, 2012 to submit the 14-count carton labeling. A June 26, 2012 amendment, submitted in response to our June 04, 2012 information request, clarified that the 2-count carton is to be marketed retail (i.e., not a sample size).and that MCC did not plan to market the OTC product with an OTC consumer information leaflet (CIL).

<b>Submitted Labeling</b>	<b>Representative of Following SKUs</b>
1-count Immediate container (Pouch)	The same one count pouch will be used for each package size.
4-count Carton	2- and 8- count Carton
10-count Carton (8 plus 2 bonus)	none
14-count Carton	13- 15-count Carton
14-count Club Store Pack Backer Card	13- and 15- count Club Store Pack
14-count Club Store Backer Card (showing carton principal display panel)	13- and 15- count Club Store Pack

## II. REVIEWER'S COMMENTS

### A. 4- (representative of 2-, 8-), 10- and 14- (representative of 13-, 15-) count cartons

#### i. Outer Carton Label Outside Drug Facts

##### Primary Display Panel

- a. The PDP has a pink background with a white rectangle in the center. On the middle of the PDP there is the following statement in blue: **“Full Prescription Strength”**. The sponsor explains that this statement indicates to the consumer that the same strength Oxytrol, that was available as a prescription product is available to the consumer over-the-counter.

**Comment: This statement is truthful and not misleading, therefore is acceptable.**

- b. For the 4- and 14-count cartons, the PDP’s top left corner shows a yellow flag with following letters in blue: **“New !”**.

**Comment: This is not acceptable. A New! flag may be acceptable if truthful and nonmisleading. However, in order for the New! flag to be truthful and nonmisleading; it must specify the aspect of the product that is new. Please communicate to the sponsor that the New! flag must be revised to specify the aspect of the product that is new or delete it from the PDP.**

- c. For the 10-count carton (8 plus 2 free), there is a yellow banner across the top of the PDP, with the statement in blue letters “25% More Free”.

**Comment: This is not acceptable. Calculation of how many transdermal systems and the number of days’ supply may be complex and potentially misleading to some consumers. In accordance with Section 502(a) of the Federal Food, Drug, and Cosmetic Act (FD & C Act), the sponsor must revise the carton label to clearly communicate to consumers the quantity of free transdermal systems. Alternatively, provide data that demonstrate that consumers understand that the proposed PDP offers 2 free transdermal systems.**

- d. The proposed proprietary name of the product is located near the center of the PDP as follows:

“(silhouette of a woman) OXYTROL for Women”

**Comment: From an IDS perspective, the location, font, color and size of the proposed proprietary name are acceptable. The proprietary name itself is conditionally acceptable (see Division of Medication Error and Prevention Analysis review of June 22, 2012).**

- e. In the PDP’s top half, above the proprietary name, beneath the “Full Prescription Strength” statement, “OXYBUTYNIN TRANSDERMAL SYSTEM 3.9MG/DAY” with the statement “Overactive Bladder Treatment” appears.

**Comment: This is not acceptable. For the OTC PDP, 21 CFR 201.61 requires that the statement of identity consisting of the established name of the drug followed by a statement of the pharmacologic category follow the proprietary name and also requires that the font “shall be in a size reasonably related to the most prominent printed matter.”**

**Therefore, please communicate to the sponsor the following:**

- 1) Move the statement of identity to follow the proprietary name**
- 2) Increase the prominence of the dosage form and strength by using a heavier darker font**
- 3) Revise the statement of the product strength from 3.9MG/DAY to read 3.9 mg/day so that there is a space between the number 9 and the letter “m”. We also recommend revising from upper case to title case to improve readability.**

- f. A prominent pink banner with yellow font, located below the proprietary name reads “Relief from Overactive Bladder”.

**Comment: Promotional statements such as this related to the use of the product are generally acceptable as long as they are truthful and not misleading, however final wording of such a statement is related to the acceptability of the proposed use.**

**We recommend that the font size “be in a size reasonably related to the most prominent printed matter” therefore, we recommend that the sponsor reduce the font size and relocate such a promotional statement. From an IDS perspective, the banner as displayed is not acceptable. Please communicate to the sponsor to reduce the font size of the banner’s text and to relocate this information somewhere in the lower right or left package quadrants.**

- g. In the 4-, 10-, and 14-count, lower left corner, to the left of “1 Patch Treats for 4 Days/4 Nights,” is a graphic image of the moon, sun and stars.

**Comment: The use of the graphic and statement communicates and reinforces to the consumer of how long one patch treats. Therefore, this is acceptable.**

h. **Declaration of net quantity**

On the lower right side of the 4-count carton PDP, under a graphic image of a patch within a half circle, reads “4 patches/16-Day Supply.”

On the lower right side of the 10-count PDP, under a graphic image of a patch within a half circle, reads “8-10-patches/40-Day Supply”/

On the lower right side of the 14-count carton PDP, under a graphic image of a patch within a half circle, reads “14 patches/56-Day Supply”.

**Comment: These meet the Declaration of Net Quantity of Contents under OTC general labeling requirements (21 CFR 201.62), therefore; are acceptable**

i. Flaps

Flaps (top, left, and right) of the carton have the product name “Oxytrol for Women” with a silhouette of a woman standing against the letter “O” of the name. The bottom flap has a barcode. **Comment: This is acceptable.**

j. Back panel is Manufacturer information

©Copyright & Distributed by MSD Consumer Care, Inc., PO Box 377, Memphis, TN 38151 USA, a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ USA. All right reserved.

**Comment: This is acceptable.**

**Country of origin:** Product of Switzerland.

**Comment: This is acceptable in accordance to 19 CFR 102 Rules of Origin.**

**ii. Outer Carton Drug Facts Label**

The Drug Facts on each carton have identical content regardless of count size. The different sections include the following:

a. **Active ingredient (in each patch):** “Oxybutynin transdermal system 3.9 mg/day”  
**Comment: This is acceptable.**

b. **Purpose:** “overactive bladder treatment”.

**Comment: This is not acceptable. Drug Facts format requires that the first letter of the first word of the purpose statement be upper case. Acceptability of the proposed purpose itself will be determined by the medical officer. Please communicate to the sponsor that the first letter of “overactive” in the purpose statement must be revised to uppercase “O”.**

c. **Use**

**Use**

- treats overactive bladder in women
- you may be suffering from overactive bladder if you have had 2 or more of the following symptoms for at least 3 months:
  - urinary frequency (the need to urinate more often than usual; typically more than 8 times in 24 hours)
  - urinary urgency (a strong need to urinate right away)
  - urge incontinence (leaking or wetting yourself if you cannot control the urge to urinate)

**Comment: From an IDS perspective, such statements are consistent with the proposed use/purpose of the proposed product and would be acceptable; however final acceptability and wording will be determined during labeling discussions.**

d. **Warnings**

**1. Other warnings**

**Warnings**

**Frequent urination can also be caused by:**

- urinary tract infections (UTI)
- diabetes
- early pregnancy
- other more serious conditions

**If you think you might have one of these conditions, see your doctor before use.**

**Comment:** The patch is a topical product, not intended for ingestion; therefore the “External Use Warning” would apply under 21 CFR 201.66(c)(5)(i). It is not present; therefore the lack of this warning is not acceptable. Please communicate to the sponsor that the following text must appear directly below the “Warnings” heading: “For external use only”.

These highlighted statements emphasize possible pre-existing conditions for which a consumer should see a doctor. Although these statements or like statements could be placed under the “Ask a doctor before use if you have” subheading as required under 21 CFR 201.66(iv), the nature of their importance may indicate that they appear as listed and highlighted under the Warnings heading. Under 21 CFR 201.66(e), FDA on its own initiative, or at the request of a sponsor, may exempt based on particular circumstances presented, one or more specific requirements set forth in 201.66(a) through (d), on the basis that the requirement is inapplicable, impracticable, or contrary to public health or safety.

Final determination of the exact wording and final list will occur during labeling meetings.

## 2. Contraindications subheading

**Do not use if you**

- **have any of these symptoms, which could be the sign of a UTI or other serious condition. See your doctor as soon as possible if you have:**
  - pain or burning when urinating. These symptoms may also be accompanied by a fever or chills.
  - blood in your urine
  - unexplained lower back or side pain
  - urine that is cloudy, or foul-smelling
- are male
- are under the age of 18
- only experience accidental urine loss when you cough, sneeze or laugh, you may have stress incontinence. This product will not work for that condition.
- have been told by a doctor you have urinary retention (are not able to empty your bladder)
- have been told by a doctor you have gastric retention (your stomach empties slowly after a meal)
- have narrow-angle glaucoma
- are allergic to oxybutynin

**Comment:** The proposed contraindications statements communicate the proposed absolute contraindications and situations not to use the drug product consistent with the types of statements expected for oxybutynin. Therefore, from an IDS perspective, such contraindications statements under 201.66(c)(5)(iii) are acceptable, however final acceptability and wording will be determined during labeling discussions.

### 3. Pre-existing conditions and certain symptoms subheading

**Ask a doctor before use if you have**

- risk factors or symptoms of diabetes, such as:
  - a history of diabetes in your immediate family
  - excessive thirst
  - extreme hunger
  - increased tiredness
- unexplained weight loss
- a history of kidney stones
- liver or kidney disease

**Comment:** From an IDS perspective, such pre-existing conditions and/or certain symptoms statements are acceptable under 21 CFR 201.66(c)(5)(iv), however final acceptability and wording will be determined during labeling discussions.

### 4. Drug-drug or drug-food interactions subheading

**Ask a doctor or pharmacist before use if you are**

- taking a prescription medication for overactive bladder
- taking a diuretic (commonly called water pills)

**Comment:** From an IDS perspective, the listing of drug-drug interactions is acceptable under 21 CFR 201.66(c)(5)(v).

However, please communicate to the sponsor that we recommend deleting the word “taking” as the first word in each bulleted drug-drug interaction and instead inserting the word “taking” immediately after the subheading (i.e., after “are”). Please note the “taking” must be in regular font (i.e., not bolded).

Final acceptability and wording will be determined during labeling discussions.

**5. Side effects or activity(ies) to avoid subheading****When using this product**

- you may see mild redness when the patch is removed, this usually goes away in several hours
- sleepiness, dizziness or blurred vision may occur
- drinking alcohol may increase sleepiness
- use caution when driving a motor vehicle or operating machinery

**Comment: From an IDS perspective, the proposed list of potential side effects or activities to avoid is acceptable under 21 CFR 201(c)(5)(vi). Final acceptability and wording will be determined during labeling discussions.**

**6. Toxicity or other reactions subheading****Stop use and ask a doctor if**

- you are not able to empty your bladder (urinary retention)
- condition worsens, or if new symptoms appear
- condition does not improve after 2 weeks of use
- you have an allergic reaction to this product
- you have severe redness, itchiness or blistering at the site of application

**Comment: From an IDS perspective, the proposed list of potential toxicities or potential other reactions that could potentially occur is acceptable under 21 CFR 201(c)(5)(vii). Final acceptability and wording will be determined during labeling discussions.**

**7. Pregnancy/breast-feeding warning and Keep out of reach of children warning**

**If pregnant or breastfeeding, ask a health professional before use.**

**Keep out of reach of children.** If swallowed, get medical help or contact a Poison Control Center right away.

**Comment: The pregnancy or breast-feeding warning is acceptable. The “Keep out of reach of children” warning is acceptable and the accompanying accidental overdose/ingestion warning is acceptable.**

*e. Directions*

**Directions**

women 18 years of age and older:

**How to use the patch:**

- open individual pouch and apply immediately to a clean, dry and smooth area of skin on your abdomen, hips or buttocks. Do not put the patch on oily, damaged (cut or scraped), or irritated (rashes) skin. Do not put the patch on skin with oils, lotions or powders because that could keep the patch from sticking to your skin.
- wear patch under clothing, do not expose the patch to sunlight
- do not cut the patch into smaller pieces
- wear only 1 patch at a time for 4 days in a row
- after 4 days, remove the used patch and apply a new one
- continue to change the patch every 4 days for as long as you use this product
- each time you put on a new patch, you should change the place where you put it (*i.e.*, *abdomen, hips or buttocks*) to avoid possible skin irritation

**How to dispose of a used patch:**

- when you take off a used patch, fold it in half with the sticky sides together
- throw it away so that it cannot be worn or swallowed by another person, especially a child, or a pet

**Comment: From an IDS perspective, the proposed directions for use and for patch disposal are acceptable. Final acceptability and wording will be determined during labeling discussions.**

*f. Other information*

**Other information**

- product comes in individual sealed pouches, do not use if pouch is torn or opened
- store between 20° to 25°C (68° to 77°F)
- protect from moisture and humidity
- do not store outside the sealed pouch

**Comment: The first proposed bulleted statement complies with the required tamper-evident packaging requirements for OTC drug products under 21 CFR 211.132, therefore is acceptable. The other three bulleted statements are storage statements and are found acceptable (see ONDQA review of November 16, 2012).**

**Because the complete Drug Facts labeling is only available on the carton, we recommend and request communication that the sponsor insert another bullet as the new second bulleted statement to encourage the consumer to “[bullet] keep the carton. It contains important information”.**

*g. Inactive ingredients*

***Inactive ingredients***

acrylic adhesive and triacetin delivered on a polyester/ethylene-vinyl acetate film

**Comment: Under 201.66, *Inactive ingredient* means any component other than an active ingredient and must be listed in alphabetical order, therefore, as listed, this is not acceptable. Other transdermal products are an example of how this is done. Please communicate to the sponsor that the inactive ingredients must list all inactive ingredients and that they must be in alphabetical order. Also see ONDQA review of November 16, 2012.**

*h. Questions or comments?*

*Questions or comments?*

call toll-free: **1-800-252-7484** between 8:00 AM and 5:00 PM Central Standard Time, Monday through Friday

**Comment: The Questions or comments? section is acceptable.**

*i. Format Specifications*

The bullet specifications are in 4.5 point.

**Comment: Please communicate that the sponsor must revise the bullet size to the required 5-point bullet size in accordance with 21 CFR 201.66 (Appendix A to Part 201). Additionally, we recommend that where ever you use a serial list before a conjunction (e.g., and, but, or), that you insert a comma before the conjunction.**

**iii. Immediate Container Label (The same one count pouch will be used with each package size)**

**Front panel**

**Please see recommendations under II.A. i. a., d., e., f., and g.**

**Recommendations for the immediate container are identical in the referenced sections.**

- a. On the top left side instructions to open the pouch are indicated in blue letters "Fold at line and tear at arrow".

**Comment: The opening instructions are acceptable.**

- b. Under the statement "Relief from Overactive Bladder" is the following bolded statement: "Product comes in individual sealed pouches, do not use if pouch is torn or opened".

**Comment: The description statement is acceptable. The tamper evident statement complies with the required tamper-evident packaging requirements for OTC drug products under 21 CFR 211.132, therefore is acceptable.**

- c. The storage information follows: The recommended temperatures for storage (20° to 25°C, 68° to 77° F)The requirements to protect from moisture and humidity and not to store out outside the pouch

**Comment: this is acceptable. See ONDQA review.**

Back Panel of the pouch has the following:

1. At the top of the back panel it has the following statement:

**“Retain outer carton for complete Drug Facts information  
DO NOT OPEN POUCH UNTIL READY TO USE”**

**Comment: This is acceptable.**

2. The next section contains the highlighted yellow warnings statements from Drug Facts, followed by a Keep out of reach of children warning. Complete Directions follow, then Questions or comments?, and manufacturer information.

**Comment: The back panel text is in agreement with the proposed Drug Facts label. This is acceptable. Consider inserting the topical use warning below the title “Warnings.”**

**Comments: The statements are in agreement with the proposed Drug Facts label. This is acceptable.**

3. The section **“Questions and Comments”** indicates the phone number to call and the hours you can do so: 1-800-252-7484 between 8:00 am and 5:00 pm Central Standard Time, Monday through Friday

**Comment: This is acceptable.**

4. The name of the distributor and the country of origin are also stated.

Distributor: MSD Consumer Care Inc.

Product of Switzerland.

**Comment: This is acceptable in accordance to 21CFR 201.1 (Name of Distributor) and 19CFR 102 (Rules of origin). See section II.A.i.j.**

5. On the lower right corner there is space to include the expiration date and the lot number.

**Comment: This is acceptable and in accordance with 21CFR201.17 and 211.166**

#### **Consumer Information Leaflet**

In a June 25, 2012 minor amendment, the sponsor, in response to the Agency’s June 4, 2012 Filing Communication letter, clarified that MCC does not plan to market the over-the-counter product with an OTC consumer information leaflet (CIL). All the labeling for women to self-diagnose overactive bladder and to subsequently use the product are contained in the Drug Facts.

**Comment: From the view point of the IDS, this is acceptable. However, we are aware that a CIL was recommended by the Advisory Panel convened on November 9, 2012. We are pending receipt of a proposed CIL.**

**C. 14-count Club Pack (Representative of the 13- and 15-count Pack)**

This component is a card printed on both sides. The front of the card contains the PDP information. The front of this card has a front window, through which the principal display panel of the 14 count carton will appear. The back of this card will contain the Drug Facts and other back panel information.

Please see recommendations under II.A.i. a., d., e., and g. Recommendations for the Club Pack are identical in the referenced sections.

**i. Label Outside the Drug Facts:**

- a. A flag with the statement: “New! 14 patches = 56-Day Supply” is on the top side of the carton and will appear for six months after the product’s introduction.

**Comment: This is not acceptable. A New! flag may be acceptable if truthful and nonmisleading. However, in order for the New! flag to be truthful and nonmisleading; it must specify the aspect of the product that is new. Please communicate to the sponsor that the New! flag must be revised to specify the aspect of the product that is new or delete the flag from the PDP.**

**The “Relief from Overactive Bladder is placed below the woman silhouette on the PDP, above the clear window. This is acceptable is allows space for the location of the window through which the 14-count Carton is seen,**

- b. The back panel has the following manufacturer information:  
Distribute by MSD Consumer care, Inc., P.O. Box 377  
Memphis, TN 38151 USA (Subsidiary of Merck & Co., Whitehouse Station, NJ USA.  
Product of Switzerland.

**Comment: this is acceptable in accordance to 21CFR 201.1 (Name of Distributor) and 19CFR 102 (Rules of origin).**

**ii. Outer Carton Drug Facts Label**

**Comment: Drug Facts content on each carton are identical, regardless of count size. Refer to section II.A.ii.**

**III. RECOMMENDATIONS:**

**Please communicate the following to the sponsor.**

**A. The following revisions must be made by the sponsor**

**Non Drug Facts Labeling**

a) 2-,4-,8-,13-,14-,15-count carton package size, and 13-,14,15-count club pack size  
The New! flag must be revised to specify the aspect of the product that is new or consider deleting it from the PDP

b) 2-,4-,8-,10-13-,14-,15-count package size, and 13-,14,15-count club pack size, and 1-count pouch  
The statement of identity and purpose statement must be moved to follow the proprietary name and to increase the prominence of the dosage form, and strength by using a heavier, darker font. Revise the statement of the product strength from 3.9MG/DAY to read 3.9 mg/day so that there is a space between the number 9 and the letter “m”. We also recommend revising from upper case to title case to improve readability.

c) 10-count carton  
The 25% More Free must be revised to clearly communicate to consumers the quantity of free transdermal systems. Alternatively, provide data that demonstrate that consumers understand that the proposed PDP offers 2 free transdermal systems.

d) 2-,4-,8-, 10-13-,14-,15-count package size, and 1-count pouch  
Reduce the font size of the central banner’s text and relocate this information somewhere in the lower right or left package quadrants.

**Drug Facts Label**

- e. Revise the first letter of “overactive” in the purpose statement to uppercase “O”.
  - f. Insert the following text directly below the “Warnings” heading: “For external use only”.
  - g. Revise Drug Facts font specifications so that the bullet size is the required 5-point in accordance with 21 CFR Appendix A to Part 201.
  - h. List all inactive ingredients and list in alphabetical order.
- B. We also recommend that the sponsor make the following revisions:
1. Under Drug Facts Warnings, Ask a doctor or pharmacist before use if you are, the sponsor should delete the word “taking” as the first word in each bulleted drug-drug- interaction and instead insert the word “taking” immediately after the subheading.
  2. Drug Facts, Other information – insert another bullet as the new second bulleted statement to encourage the consumer to “[bullet] keep the carton. It contains important information”.

3. We recommend that where ever you use a serial list of items, insert a comma before a conjunction (e.g., and, but, or).
4. On the pouch backside, consider inserting the “topical use warning” below the title “Warnings.”

#### **IV. SUBMITTED LABELING**

The labels on the remaining pages of this labeling review were submitted on March 26 and September 04, 2012 and were evaluated in this labeling review:

6 Page(s) of Draft Labeling have been Withheld in Full as  
b4 (CCI/TS) immediately following this page

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

/s/  
-----

MARIA E YSERN  
11/27/2012

RUTH E SCROGGS  
11/27/2012



**SOCIAL SCIENTIST'S REVIEW**

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Nonprescription Clinical Evaluation (DNCE)  
Office of Drug Evaluation 4

**NDA:** 202211  
**Sponsor:** Merck  
**Subject:** Oxytrol OTC – Label Comprehension and Self-Selection  
**Drug Name:** Oxybutynin  
**Product Name:** Oxytrol for Women  
**Proposed Indications:** Treats overactive bladder in women  
**Dosage Form:** Patch  
**Route of Administration:** 3.9 mg/day Transdermal system  
**Date of Submission:** March 26, 2012  
**Date of Review:** November 1, 2012  
**Reviewer:** Barbara R. Cohen, MPA  
**Team Leader:** Lesley-Anne Furlong, M.D.

**Table of Contents:**

I) Background..... 3

II) Summary of Label Comprehension and Self-Selection Studies Submitted by the Sponsor..... 3

III) Conceptual Framework for Review ..... 4

IV) Pivotal Label Comprehension (10053)..... 4

V) Label Comprehension Among Female OAB Sufferers 65+ (92101) ..... 14

VI) Label Comprehension – Diabetic Warnings Among the OAB Population (92099) ..... 15

VII) Label Comprehension – Enhanced Pregnancy Warning among Women of Childbearing Age (92062) ..... 17

VIII) Label Comprehension – Female OAB and non-OAB Sufferers, Males (82023) ..... 18

IX) Self-Selection, Pregnant Women with OAB Symptoms (10054).....20

X) Self-Selection in Men with OAB Symptoms (92061) ..... 21

XI) Self-selection/Self diagnosis study in women with OAB symptoms; also four other subpopulations: men, diabetics, those with glaucoma; and those pregnant or nursing (2008-19). 22

XII) Final Discussion, Conclusions and Recommendations..... 25

XIII) Appendices.....31

## **I) Background:**

This review evaluates the label comprehension and self-selection studies that were submitted as part of the consumer behavior studies in support of the partial Rx-to-OTC switch of Oxytrol, a treatment for overactive bladder. The proposed product, Oxytrol for Women, would be indicated for women only, in order to obviate clinical concerns about men using an OTC product and thereby delaying a diagnosis of prostate disease. The actual use study that was submitted as part of the NDA is reviewed by the DNCE Medical Officer in a separate document.

As part of the NDA submission, the Sponsor submitted five label comprehension studies and three self-selection studies, all conducted during the timeframe of 2008 to 2011. The Sponsor began meeting with FDA in 2007 on this switch; although several potential consumer studies were discussed during this time period, FDA did not have the opportunity to review the protocols of most of the label comprehension and self-selection studies that were eventually part of the NDA submission.

## **II) Summary of Label Comprehension and Self-Selection Studies Submitted by the Sponsor:**

- Pivotal label comprehension study– conducted in late 2010.
- Label comprehension study with age 65+ self-reported overactive bladder (OAB) sufferers – conducted in early 2010.
- Label comprehension study of diabetic warnings among general OAB sufferers – conducted in early 2010.
- Label comprehension study of enhanced pregnancy warning among women of childbearing age – conducted in early 2010.
- Label comprehension study among NL (normal literacy) female OAB sufferers, LL (low literacy) female OAB sufferers, general population female non-sufferers, and men – conducted in 2008.
- Self-selection study in pregnant women with OAB symptoms – conducted in late 2010.
- Self-selection study in men with OAB symptoms – conducted in late 2009.
- Self-selection study in women with OAB symptoms; also four other subpopulations: men, diabetics, those with glaucoma, and those pregnant or nursing – conducted in early 2009.

The pivotal label comprehension study is the research of the most intense focus here.

This is not only because it is the most recent and rigorous research, but also because the other label comprehension studies were somewhat more exploratory in nature; moreover, the previous research was based on earlier versions of labels that were subsequently tweaked as a result of research findings. Nonetheless, earlier studies are also discussed, primarily with regard to relevant findings that either help to fill in gaps of what was not assessed in the pivotal study, or else to provide further insights into findings from that study.

### **III) Conceptual Framework for Review:**

In examining the DARRTS file of FDA-Sponsor discussions and reviews on this product switch since 2007, I identified eight key medical issues relatively specific to this product that emerged from the various discussions. Other issues also of importance regarding this product are more standard on Drug Facts Labels - such as allergies to the active ingredient or how long to take the drug if there is no sign of symptom improvement, or more standard with respect to transdermal patch use - such as how to use the patch, and what to do if there is a skin reaction. Therefore, I discuss the relevant study findings on these issues but they are not the focus of the analysis.

#### Summary of Key Medical Issues

- Consumer self-identification of OAB
- Urinary retention warning
- Gastric retention warning
- Diabetes risk
- UTI
- Pregnant Women
- Men
- Elderly

### **IV) Pivotal Label Comprehension (Study #10053) – Conducted in late 2010:**

#### **A) Overall Methodology:**

- Cohort 1 – females 18 + with self-reported OAB, general population, n=472
- Cohort 2 – females 18+ with self reported OAB, low literacy augmentation, n=120
- Cohort 3 – females 44+ with self reported risk of diabetes symptoms, n=160

The pivotal label comprehension study (LCS) was conducted in nine geographical sites dispersed throughout the United States and its focus spanned several, but not all, of the key medical issues above. Cohorts 1 and 2 were asked identical questions, ranging from OAB self-identification, to urinary and gastric retention, to other issues such as allergy to oxybutynin. (See Appendix 1 for the questionnaires). Many, but not all questions reflected primary communications objectives as determined by the Sponsor. The objective of Cohort 3 was to assess comprehension of diabetes risk specifically among consumers who were at risk of diabetes but who had not been diagnosed yet as having diabetes or pre-diabetes.

Cohort 3 was asked two diabetes-related questions that were not asked of Cohorts 1 and 2. There were three other questions asked of Cohort 3 that were also asked of Cohorts 1 and 2. The Sponsor stated that these three questions were inserted so as to mask the true intent of the Cohort 3 questionnaire. Nonetheless, since the responses provide additional insights into other pivotal LCS objectives, I have analyzed those responses as well.

Potential respondents were recruited through market research facility databases. They were screened for qualifications over the telephone and if qualified and interested, they were invited to come to the research facility for an interview. In addition to the standard screening questions, subjects who were recruited for Cohort 3 were taken through a Diabetes Risk Calculator during the telephone screening process. This calculator was adapted from an online tool sponsored jointly by the American Diabetes Association and GlaxoSmithKline. The components of the online calculator tool included: gender, age, ever experienced gestational diabetes, ethnicity, diagnosed by a doctor with hypertension, and weight and height to derive BMI. If subjects were over age 57, they were also asked if they had an immediate family member with diabetes and they were also asked about their activity level. During the screening process, subjects were asked to provide their weight range and height; the midpoint of the weight range was then input into the Diabetes Risk Calculator. Once onsite, Cohort 3 subjects were rescreened, which included measuring their weight and height, and self-administration by the consumer of the Diabetes Risk Calculator.

Following administration of the REALM (literacy assessment), respondents were provided with a full mock up of the Oxytrol package and the interviewer left the room. Subjects read the exterior package label and Drug Facts Label at their own pace. When they were finished, the interviewer returned and administered the label comprehension interview. The questionnaire consisted of open-ended, mostly scenario-based questions based on uses and warnings contained on the label, which mostly corresponded to communications objectives.

*Social Science Comments:*

*This pivotal LCS was conducted not with an all-comers population, as the FDA's Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products recommends, but rather with targeted populations of female OAB sufferers and female age 44+ who were at risk for diabetes (with and without OAB). Because of the medical issues relevant to Oxytrol for Women, there could be a reasonable case made as to why this was not an all comers study. Since it was not an all comers study, there were and are gaps in what the total holistic picture of all the research reveals with regard to the potential comprehension of the average person picking up this product from the shelf and wondering if it is for them. The first LCS conducted in 2008 had elements of an all comers study. However, as will be discussed, because of the methodological issues in that study the findings cannot be definitively relied upon.*

*One definite problem with the pivotal study was that there was only a 6% low literacy representation in Cohort 1, which was the general population by which the target threshold was measured. FDA's Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products states that there are estimated 25-30% low literates in the population and recommends that they be adequately represented in the study sampling. Some Sponsors have maintained that they cannot hit this number in random sampling*

*without explicitly recruiting for an augmented enriched low literacy cohort. However, 6% is far below even what most Sponsors usually maintain is possible in random sampling. To reiterate, this particular study was recruited not through mall intercepts, but through telephone lists maintained by the marketing research facilities that were associated with this study. Because often the consumer products companies who are customers of these facilities are looking to conduct research with target consumers having certain minimum thresholds of discretionary spending capability, the lists maintained by these facilities are not always representative of the general population, particularly if they are located in relatively upscale geographic areas that are not highly accessible to mass transportation. Indeed, the respondents for the augmented low literacy Cohort 2 were not generated from the same sites as Cohort 1; rather, they were recruited from just two other sites that were solely dedicated to filling the augmented low literacy cohort. Thus, not only was the general sample not representative of the general population, but the low literacy augmented sample was probably not representative of the low literacy population as whole.*

*The result of all of this is that – because low literacy respondents often may have more trouble than normal literacy respondents in comprehending certain aspects of labels – the ability of a particular communications threshold to meet or surpass a target threshold may have been upwardly biased in the results reported out from this study. In other words, there is the potential that study results represent best case results; this caveat also holds for the other consumer studies that do not have adequate representation of the low literacy population in their target threshold measurements or, more broadly, in their total sample.*

*In addition to the low literacy representation in Cohort 1, Cohort 3 also had small low literacy representation – 10%. In the case of Cohort 3 (unlike Cohort 1) there was no associated augmented cohort with which to provide insights into normal literacy (NL) vs. low literacy LL differences, if any. This is a concern given that the focus of Cohort 3 was to understand comprehension of the diabetes risk warnings among those who were at risk for diabetes. Since diabetes is often a high concern with special populations, the issue here is that the scores of the two diabetes questions may be upwardly biased due to the relatively higher literacy of the surveyed population for this threshold.*

*The results of the two diabetes questions also may be upwardly biased in this study because of the diabetes risk calculator that was administered to subjects as part of the rescreening process immediately before they were administered the survey at the market research site. Note that the recruiting specifications were targeted to those who had not been told by a doctor that they had diabetes or pre-diabetes, but who had self-reported some risk predictive of pre-diabetes or undiagnosed diabetes as assessed through an online risk calculator. While it's common practice to rescreen subjects prior to interviews, the nature of this particular risk calculator could have – intentionally or unintentionally – cued subjects that the survey was going to focus on diabetes related issues, which could have in turn caused them to hone in on that aspect of the label more than they otherwise would have.*

## **B) Communication Objectives of Pivotal Study and Associated Medical Consequences:**

The primary objectives of Cohorts 1 and 2 were to measure respondent comprehension of the warnings for the following communication objectives:

- 1) Use:
  - a. You may be suffering from overactive bladder if you have had two or more of the following symptoms for at least 3 months:
    - i. Urinary frequency (the need to urinate more often than usual; typically more than 8 times in 24 hours).
    - ii. Urinary urgency (a strong need to urinate right away)
    - iii. Urge incontinence (leaking or wetting yourself if you cannot control the urge to urinate).
- 2) Warnings:
  - a. Do not use if you:
    - i. Only experience accidental urine loss when you cough, sneeze or laugh, you may have stress incontinence. This product will not work for that condition.
    - ii. Have urinary retention (are not able to empty your bladder)
    - iii. Have been told by a doctor that you have gastric retention (your stomach empties slowly after a meal)
    - iv. Narrow-angle glaucoma
    - v. Are allergic to oxybutynin.
  - b. Ask a doctor before use if you have:
    - i. A history of kidney stones
    - ii. Liver or kidney disease
  - c. Ask a doctor or pharmacist before use if you are:
    - i. Taking a diuretic (commonly called water pills)
  - d. Stop use and ask a doctor if:
    - i. You have an allergic reaction to this product
    - ii. You have severe redness, itchiness or blistering at the site of application.

The primary objectives for Cohort 3 were to measure consumer comprehension of the objective relating to the diabetes warning among consumers who self-reported risk factors and also qualified for the cohort via the use of an online risk calculator:

- 1) Warnings:
  - a. Ask a doctor before use if you have:
    - i. A history of diabetes in your family.
    - ii. Frequent urination with excessive thirst, extreme hunger or

increased tiredness. These could be early signs of diabetes.

All primary objectives were categorized based on higher versus lower medical consequence, as determined by two Sponsor physicians. Risk classifications were as follows:

Higher Medical Consequences (Sponsor set target threshold at 90%)

- Have urinary retention (not able to empty your bladder)
- Have been told by a doctor that you have gastric retention (your stomach empties slowly after a meal)
- Narrow angle glaucoma
- Allergic to oxybutynin
- Allergic to this product
- You have severe redness, itching or blistering at the site of application.

Lower Medical Consequences (Sponsor set target threshold at 85%)

- You may be suffering from OAB if you have had two or more of the following symptoms for at least three months:
  - Urinary frequency (the need to urinate more often than usual; typically more than eight times in 24 hours)
  - Urinary urgency (a strong need to urinate right away)
  - Urge incontinence (leaking or wetting yourself if you cannot control the urge to urinate)
- Only experience accidental urine loss when you cough, sneeze or laugh, you may have stress incontinence. This product will not work for that condition.
- A history of kidney stones
- Liver or kidney disease
- Taking a diuretic (commonly called water pills)
- Undiagnosed diabetes

Cohorts 1 and 2 were presented with scenarios about all of the communications objectives except diabetes. Cohort 3 was asked about family history of diabetes, frequent urination/excessive thirst as well as product use, foul smelling urine, OAB symptoms and stress incontinence. The Sponsor asserted that the last four topics were used solely to mask the purpose of the diabetes target. Nonetheless, since these questions provide an additional opportunity to analyze consumer comprehension on these topics, I have discussed them in this review.

Before moving to the findings, it's important first to examine the Sponsor's stated communications objectives above and assess to what extent they were actually measured in the Pivotal Label Comprehension Study:

- Communication Objective: You may be suffering from OAB if you have had two or more of the following symptoms for at least three months:
  - Urinary frequency (the need to urinate more often than usual; typically more than eight times in 24 hours)
  - Urinary urgency (a strong need to urinate right away)

- Urge incontinence ( leaking or wetting yourself if you cannot control the urge to urinate)

This objective was actually divided into two separate questions in the Pivotal LCS:

Q.3: For the past 4 months, Betsy has had to urinate more often than usual, about 9 times every 24 hours. She has also had several leaking accidents. She has no other medical conditions. Betsy would like to use this product. Is it okay or not okay for Betsy to use this product?

Q.6: According to the label, for how long should you have symptoms of overactive bladder before trying the product?

Only Q.6 – minimum length of symptom duration - was applied to a target threshold. Thus, when the Sponsor asserts that this communication objective came within a point of meeting the 85% target threshold, this only refers to comprehension of minimum length of symptom duration. It does not refer to specific symptom recognition.

Social Science Comments:

*It is difficult to test the entire complex communication objective in one question, so I don't disagree with parsing it out. Perhaps the label could have depicted the information differently to begin with, but given how it read, I concur with the Sponsor's decision to split it into two questions. Consider that if consumers understand that they should have symptoms for at least three months before they use the product, and if they then behave in that manner, that might lessen any delays due to missed diagnosis as the real conditions would presumably become more apparent. So – it makes sense to make the 3 months minimum symptom duration its own question.*

*Note that Q.6 was not a scenario question but a straightforward, fact type of question "According to the label, for how long could you have symptoms of overactive bladder before trying the product?" The question was not misleading but did cue respondents to check the label before answering and also was easier to answer because it involved just one aspect of symptoms and didn't require respondents to analyze a particular situation. In real life, if people are thinking about using a product, the length of current symptom duration is certainly one factor but not the only factor in thinking about whether it is right for them. Therefore, if they are going to the label to seek relevant information, they are not going to only look at that aspect of the label.*

*Moreover, the Sponsor should have made clearer in the study report about what specific parts of this communications objective the question did and did not measure. A casual reading of this report would not turn up this information.*

*Finally, since undiagnosed diabetes was a key medical concern and a three month minimum wait to try this product might lessen a delay to diagnosis, this measure*

*might have been useful to assess in Cohort 3. The Sponsor chose not to do so.*

- Communication Objective: Ask a doctor before use if you have:
  - A history of diabetes in your family. Frequent urination with excessive thirst, extreme hunger or increased tiredness. These could be early signs of diabetes.

This communication objective was partially addressed in two separate questions, both asked in Cohort 3:

Q.4: For the past five months, Megan has had to urinate frequently and urinate right away. Her mother has diabetes. Megan would like to use this product. According to the label, what if anything should Megan do?

Q.6: Rachel has been experiencing excessive thirst. She also noticed that she has been needing to urinate more often than usual. Rachel would like to use this product. According to the label, what if anything, should Rachel do?

*Social Science Comments:*

*Symptoms involving extreme hunger or increased tiredness, though part of the stated communication objectives derived from the label, in fact were not tested in this pivotal study. In fact, they were not tested in any of the studies. Again, the Sponsor should have made clearer in the study report about what specific parts of the communication objective these two questions did and did not measure. A casual reading of this report would not turn up this information.*

*Finally, it's worth noting that there were no explicit communication objectives in this study regarding UTI symptoms. Nonetheless, there was one question (asked of all three cohorts) that partially addressed UTI:*

*Q.2: Debra has symptoms of overactive bladder that she has not begun treating. Lately she noticed that her urine has been foul smelling. According to the label, is it okay or not okay for Debra to use this product?*

*This question addressed symptoms mentioned on the label, and I believe that overall, UTI symptoms should have been among the primary communications objectives that were tested in the pivotal study. As will be discussed further, comprehension of UTI symptoms was tested in a previous LCS (OAB sufferers 65+). It was also tested in separate cohorts in the initial LCS among NL female OAB sufferers and LL female OAB sufferers, but it was never tested among a combined representative general population of OAB sufferers. The pivotal study, with its general population cohort of female OAB sufferers, would have been a better way to test this aspect of comprehension (though not ideal in that its general population cohort still had sub-optimal low literacy representation).*

### **C) Response Coding and Sponsor Analysis:**

The combined initial response and follow up responses led to the following five net code categories:

- Demonstrates Full Comprehension
- Demonstrates Partial Comprehension and Understanding of Risk from Label
- Demonstrates Partial Comprehension but Insufficient Evidence of Understanding of Risk from Label
- Does not demonstrate comprehension
- Response Indicates Confusion.

#### 1) Demonstrates Full Comprehension

The respondent demonstrates correct comprehension of the objective at both the initial scenario as well as at the follow up question.

#### 2) Demonstrates Partial Comprehension and Understanding of Risk from Label

The Respondent does not specifically demonstrate correct comprehension of the objective at the initial scenario but then demonstrates a credible level of understanding of the possible risk associated with the scenario at the follow up question. Alternatively, the respondent demonstrates correct comprehension at the initial question but then provides a general response at the follow up.

#### 3) Demonstrates Partial Comprehension but Insufficient Evidence of Understanding of Risk from Label

The respondent may or may not demonstrate correct comprehension of the objective at the initial scenario and then does not demonstrate an adequate understanding of the associated risks at the follow up question.

#### 4) Does not Demonstrate Comprehension

Respondent does not demonstrate comprehension of the objective at the initial scenario or at the follow up question.

#### 5) Response indicates Confusion

The respondent is confused by the question, provides an answer to a different question or indicates that they felt that more information is required even though the interviewer had instructed them that the scenario contained all the information necessary to answer the question.

The Sponsor then analyzed the raw verbatims and determined that “correct comprehension” was comprised of responses coded as Demonstrates Full Comprehension and Demonstrates Partial Comprehension and Understanding of Risk from Label; and “incorrect comprehension” was comprised of responses coded as Demonstrates Partial Comprehension but Insufficient Evidence of Understanding of Risk from Label; Does not Demonstrate Comprehension, and Response Indicates Confusion.

Social Science Comments:

*I have reviewed the coding and basically concur with the way in which the Sponsor coded the responses.*

**D) Pivotal Label Comprehension Findings (Cohort 1 and 2):**

(Note: all results reported are the lower bound of the 95% confidence interval except where otherwise noted. See Appendix 1 for confidence interval and point estimate data)

- Consumer identification of OAB:
  - Comprehension of minimum symptom duration of 3 months before using product – 84% lower bound (one point below 85% threshold).
  - Comprehension of specific symptoms being OAB - 82% lower bound (no pre-specified threshold as this was not a communications objective).

Social Science Comments:

*Regarding the minimum three months symptom duration, there was a significant difference in comprehension when comparing the normal literates (from Cohort 1) versus low literates (from Cohorts 1 and 2): 88% vs. 71% respectively. Moreover, this question elicited the largest percentage of “don’t know” responses in the survey – at 8% - further indicating that there was confusion around this communication objective.*

*Regarding the comprehension of specific symptoms being OAB, note that Cohort 3 was also asked this question. This scored at 80% lower bound – an almost identical score to Cohort 1. Also, all relevant elements in the scenario posed in this question were more favorable than what the label indicated, so the question did not fully measure the ability of consumers to comprehend when a scenario was incorrect. A more rigorous way to pose the question would have been to lower one of the key elements and see what the impact on comprehension would have been.*

- Comprehension of do not use if urinary retention: 88% lower bound (three points below 90% threshold). There was also a significant difference between normal literates and low literates here as well: 89% vs. 75%, respectively.

Social Science Comments:

*Of note, the proposed label has since been revised to make clearer that this is referring to urinary retention that has been officially diagnosed by a doctor, and not just consumer perception of urinary retention.*

- Comprehension of do not use if diagnosed with gastric retention: 87% lower bound (three points below 90% threshold).

Social Science Comments:

*Here there was a significant difference as well between normal and low literates: 91% vs. 74% respectively.*

- Comprehension of ask a doctor if there is diabetes family history together with frequency and urgency: 83% lower bound (two points below 85% threshold). Here there was a point estimate difference of 91% NL vs 72% LL.
- Comprehension of ask a doctor if there is excessive thirst and urinary frequency – 82% lower bound (three points below 85% threshold).
- Comprehension of not okay to use if allergic to oxybutynin – 93% lower bound – (three points above 90% threshold).
- Comprehension of stop use and ask a doctor if you have an allergic reaction to this product – 91% lower bound (one point above 90% threshold).
- Comprehension of stop use and ask a doctor if develop blisters and red/itchy rash – 85% lower bound (five points below 90% threshold).

*Social Science Comments:*

*If consumers actually do develop blisters and a red/itchy rash, it appears from the actual use study that they will stop using the product.*

- Comprehension of not okay to use if have narrow angle glaucoma - 84% lower bound – (six points below 90% threshold).

*Social Science Comments:*

*Glaucoma is a condition for which warnings already exist on other OTC Drug Facts Labels, including but not limited to first generation antihistamines.*

- Comprehension of ask a doctor if have kidney stones – 87% lower bound – two points above threshold.
- Comprehension of ask a doctor/pharmacist if using diuretic – 84% lower bound – one point below threshold.
- Comprehension of ask a doctor if liver disease – 80% lower bound – five points below threshold.
- Comprehension of not okay to use if foul smelling urine – 84% lower bound. – no target threshold as this was not a communications objective. The elderly were not significantly different in comprehension than nonelderly for this question. Cohort 3 was also asked this question, and the lower bound score there was 79%.
- Note: there were no significant differences between the older population and the younger population for almost all of these questions. Comprehension of “ask a doctor if liver disease” was a communication objective in which the older

population did score less favorably than the youngest respondents – lower bound comprehension was 94% for ages 18-34 and 78% for those 60+

### **E) Summary of Pivotal LCS Findings:**

- Allergy warnings did particularly well.
- Other warnings were in 80-90% range among general population
- Comprehension of 3+ months symptoms before trying product was in 80% range but there was some upward methodological bias; there was also a significant gap between normal and low literates. Comprehension of 3+ months symptoms was, in general, a problem in the earlier LCS research, as will be discussed. For instance, in the age 65+ LCS, it scored at 74% lower bound. In the Diabetic Warnings LCS, which incorporated a two week scenario question, it scored at 41% (point estimate) and in the Enhanced Pregnancy LCS, it scored at 26% point estimate.
- Specific OAB symptom identification was in 80% range but this question had upward methodological bias as well.
- Diabetes warning results in 80-85% range among general population at risk, but there was a small low literate population, and results may have been upwardly biased due to study methodology. Also, not all aspects of the diabetes warning on the label were tested.
- UTI was only very partially addressed in this study.
- Older respondents did not have significantly less comprehension than younger respondents.
- Pregnancy was not addressed.
- Males were not addressed.

The earlier studies that are discussed below fill in some of the gaps noted above, and also provide additional insights into some of the findings that are cited above.

### **V) Label Comprehension Among Female OAB Sufferers 65+ (92101) – conducted in Early 2010:**

#### **A) Methodology:**

- One cohort, n=350

The objective of this study was to evaluate comprehension of key label messages among older female OAB sufferers. In this study, there was no augmented low literacy cohort but there were 12% low literates in the general population cohort. Participants were recruited and interviewed from seven geographically dispersed research facilities in the United States (although there were none on the East Coast). Age distribution was as follows: 53% of the participants were age 65-69; 28% were age 70 to 74; 15% were age 75-79 and 5% were 80+.

This study mirrored most of the key medical issues that were the focus of questions in the pivotal study. However, it had more questions about the variety of potential UTI symptoms

mentioned on the label and measured them against target thresholds, whereas the pivotal study only addressed one and did not measure it against a threshold. A 90% target threshold was assigned to all objectives.

Overall, “correct comprehension” was comprised of responses coded as “Demonstrates Full Comprehension” and “Demonstrates Partial Comprehension. Overall “incorrect comprehension” was comprised of responses coded as “Demonstrates Partial Comprehension but Insufficient Evidence of Understanding of Risk From Label,” “Does not Demonstrate Comprehension” and “Response Indicates Confusion.” These determinations were made by the Sponsor as a result of verbatim analysis to the follow up questions that were posed to subjects after each question – “why do you say that?”

### **B) Key Findings:**

- Comprehension of not okay to use if blood in urine – 94% lower bound
- Comprehension of not okay to use if pain while urinating – 93% lower bound
- Comprehension of not okay to use if foul smelling urine – 88% lower bound
- Comprehension of not okay to use if pain in lower back – 89% lower bound
- Comprehension of not okay to use if urinary retention – 83% lower bound
- Comprehension of not okay to use if gastric retention – 81% lower bound
- Comprehension of ask a doctor if family history of diabetes/urinary frequency – 88% lower bound
- Comprehension of ask a doctor if losing weight for no reason – 87% lower bound
- Comprehension of 3 months minimum symptom duration – 74% lower bound
- Comprehension of one patch at a time - 98% lower bound
- Comprehension of wear first patch for 4 days – 96% lower bound
- Comprehension of wear second patch for 4 days – 97% lower bound
- Comprehension of not okay if allergic to oxybutynin – 86% lower bound
- Comprehension of stop use and ask a doctor if there is an allergic reaction – 85% lower bound – but 60% completely correct and 29% partially correct
- Comprehension of ask a doctor or pharmacist if current Rx user – 88% lower bound
- Comprehension of stop use and ask a doctor if symptoms are getting worse – 96% lower bound, but this was heavily mitigated; 74% demonstrated complete comprehension and 24% demonstrated partial comprehension
- Comprehension of stop use and ask a doctor if conditions have not improved – 87% lower bound, but heavily mitigated; 48% demonstrated complete comprehension and 43% demonstrated partial comprehension.

## **VI) Label Comprehension – Diabetic Warnings Among the OAB Population (92099) – Conducted in Early 2010:**

### **A) Methodology:**

Label comprehension study of diabetic warnings among general OAB sufferers – conducted in early 2010

- Cohort 1, general population OAB sufferers 18+, n= 360
- Cohort 2, low literacy OAB sufferers 18+, n= 230

The stated objective of this study was to evaluate the effectiveness of the diabetic warnings “Ask a doctor before use if you have a family history of diabetes or frequent urination with excessive thirst, extreme hunger or increased tiredness. These could be early signs of diabetes.” However, as in the pivotal LCS, extreme hunger and increased tiredness were not the focus of any questions.

Respondents were recruited and screened by telephone and the interviews were subsequently conducted in nine somewhat geographically dispersed sites around the United States. There were only 8% low literate respondents in the general population cohort. As in the pivotal study, this potentially had the impact of upwardly biasing the findings. However, unlike in Cohort 3 of the pivotal study, which focused on diabetes, this study had an augmented low literacy cohort.

In addition to the diabetes questions, three other questions were asked (which the Sponsor deemed as unrelated to the study objective) to avoid any concern of bias by focusing the respondents just on that section. One was related to product use, one related to urge incontinence and one was the identical question to that subsequently asked in the pivotal LCS about self identification of symptoms.

## **B) Key Findings: Diabetes Risk Questions:**

Question 2: For the past 5 months, Megan has had to urinate frequently and urinate right away. Her mother has diabetes. Megan would like to use this product. What if anything should Megan do?

Lower bound – 90%; 93% NL vs 79% LL

Question 8: Over the past 3 months, Rachel has noticed that she has the need to urinate more often than usual. She is also experiencing excessive thirst. Rachel would like to use this product. According to the label, what if anything, should Rachel do?

Lower bound - 92%; 95% NL vs. 71% LL

## **C) OAB Self-Identification Questions:**

Question 4: For the past 4 months, Betsy has had to urinate frequently and has had several leaking accidents. Betsy would like to use this product. Is it ok or not ok for Betsy to use this product? (Note: This was not considered a communications objective, so no lower bound was generated to compare with a target threshold).

Question 6: Suzanne has been experiencing a strong urge to urinate and has had a few

accidents when she could not get to the bathroom quickly enough. She has been experiencing these symptoms for 2 weeks. Suzanne would like to use this product. Is it ok or not ok for Suzanne to use? Again, this was not considered a communications objective, so no lower bound was generated to compare with a target threshold.

#### **D) Relevant Findings – OAB Self Identification:**

- Comprehension of ok to use if had two of the listed OAB symptoms for 4 months – 76% point estimate.
- Comprehension of not okay to use if had two of the listed OAB symptoms for 2 weeks – 41% point estimate.

#### Social Science Comments:

*Question 6 was an attempt to assess whether consumers took away from the label that they should have OAB for at least three months prior to using Oxytrol. Given the very poor response to this question, and the fact that the Sponsor did not change the label for subsequent testing after these responses, it's not surprising that the Sponsor changed this question from a scenario asking about several items to a non-scenario question in the pivotal that pointed respondents exactly to the section of the label. Since the label did not subsequently change, it's unclear whether consumers can apply all of the different criteria at once to determine whether it is appropriate to take the product.*

### **VII) Label Comprehension – Enhanced Pregnancy Warning among Women of Childbearing Age (Study #92062) – Conducted in Early 2010:**

#### **A) Methodology:**

Label comprehension study of enhanced pregnancy warning among women of childbearing age – conducted in early 2010

- Cohort 1, general population, 18-40, n=350
- Cohort 2, low literacy, 18-40, n=224

The objective of this study was to evaluate the consumer's ability to understand that a doctor should be consulted prior to use if pregnancy is a possible cause of OAB symptoms. The target population for both the general population and low literacy cohorts consisted of females of childbearing age (18-40) who had not been surgically sterilized. The population was recruited using marketing research facility site databases. The research was conducted at nine geographically dispersed sites throughout the United States. The general population had only 8% low literates but there was an augmented low literacy cohort with which to make comparisons between normal and low literates.

In addition to the pregnancy question, three other questions were asked (which the Sponsor deemed as unrelated to the study objective) to avoid any concern of bias by focusing the

respondent on a specific section of the label. These questions related to product use, minimum age, and minimum 3 months duration of symptoms.

## **B) Key Findings:**

### Undiagnosed Pregnancy – 90% Target Threshold

- Q4: Melissa has noticed that she has had to urinate more frequently. She has also noticed that she has missed two periods. Melissa thinks this product may help with her more frequent urination. According to the label, what if anything should Melissa do?

93%, lower bound of 90% of general population said that Melissa should talk to a doctor – this met the 90% threshold.

### *Social Science Comments:*

*This question cued the respondent to think of a potential pregnancy scenario merely by virtue of having missed two periods, regardless of OAB symptoms mentioned. The reasonable response would be to speak to their doctor, regardless of any other issues, and this would have been a correct response to the question without the respondent having knowledge about the communication objective. A more effective question would have incorporated having missed one period, rather than two.*

### Minimum 3 months duration of symptoms (No target threshold as it was not a communication objective)

- Q 6. Suzanne has been experiencing a strong urge to urinate and has had a few accidents when she could not get to the bathroom quick enough. She has been experiencing these symptoms for 2 weeks. Is it okay or not okay for Suzanne to use this product?

Only 26% (point estimate) of the general population said it was not okay to use this product.

## **VIII) Label Comprehension – Female OAB and non-OAB Sufferers, Males (Study #82023) -- conducted in early 2009:**

### **A) Methodology:**

- Cohort 1, Normal literate female OAB sufferers, n=196
- Cohort 2, Low Literate female OAB sufferers, n=204
- Cohort 3, General population of female non-OAB sufferers, n=199
- Cohort 4, General population of males, n=76

The objective of the three female cohorts was to evaluate comprehension of the key safety and risk communication objectives for product use, directions for use and product warnings

found on the Drug Facts Label. The objective for cohort 4 was to evaluate whether men understood that this product is for women only. In all, there was testing of comprehension of 30 primary communications objectives and 3 secondary communications objectives for Cohorts 1, 2 and 3, and testing of comprehension of five communication objectives for Cohort 4. The three female cohorts were recruited from marketing research site databases and the male cohort was recruited via a mall intercept methodology. Interviews took place at 16 research facilities throughout the United States.

There were five categories of responses that were defined as “demonstrated comprehension”: 1) Correct initially 2) acceptable initially and correct after probe 3) acceptable initially and acceptable after the probe 4) incorrect initially and correct after probe and 5) incorrect initially and acceptable after probe

Social Science Comment:

*As noted above, there was no general population cohort of female OAB sufferers. Also, the vast array of questions in this study may have caused respondent fatigue, which could have led to repetitive, not well thought out responses to questions.*

**B) Key Findings (point estimate, lower bound of 95% confidence interval):**

- Not okay, male: NL female OAB 95% , LB 91%;  
LL female OAB 87%, LB 81%  
General female non-OAB 88%, LB 83%,  
Men 95%, LB 86%
- Not okay, blood in urine: NL female OAB 94%, LB 89%;  
LL female OAB 94%, LB 89%  
General female non-OAB 95%, LB 91%;
- Not okay, lower back pain: NL female OAB 95%, LB 91%;  
LL female OAB 91%, LB 86%  
General female non-OAB 95%, LB 90%
- Not okay, pain while urinating: NL female OAB 92%, LB 87%;  
LL female OAB 91%, LB 86%  
General female non-OAB 97%, LB 93%.
- Ask doctor/pharmacist if use Rx: NL female OAB 92%, LB 87%.;  
LL female OAB 84%, LB 78%  
General female non-OAB 95%, LB 91%
- Ask doctor if losing weight, no reason: NL female OAB 88%, LB 83%;  
LL female OAB 83%, LB 77%  
General female-non OAB 95%, LB 90%
- Ask health professional if breastfeeding: NL female OAB 82%, LB 75%;

- LL female OAB 83%, LB 77%
  - General female non-OAB 84%, LB 78%
- Wear first patch 4 days:
  - NL female OAB 99%, LB 96%;
  - LL female OAB 98%, LB 95%
  - General female non-OAB 97%, LB 93%
- One patch worn at a time:
  - NL female OAB 100%, LB 98%;
  - LL female OAB 99%, LB 96%
  - General female non-OAB 100%, LB 98%
- Stop use, ask a doctor if your condition has not improved by three weeks:
  - NL female OAB 73%, LB 66%;
  - LL female OAB 77%, LB 70%
  - General female non-OAB 69%, LB 62%
- Stop use, ask a doctor if you are getting worse after a few weeks:
  - NL female OAB 90%, LB 85%;
  - LL female OAB 88%, LB 83%
  - General female non-OAB 90%, LB 85%

**IX) Self-Selection, Pregnant Women with OAB Symptoms (10054) conducted in late 2010:**

**A) Methodology:**

- Cohort 1, females 18-40 with self-reported pregnancy and self-reported OAB, n=308
- Cohort 2, females 18-40 with self-reported pregnancy and self-reported OAB, low literacy, n=127

This study was conducted in nine market research facilities dispersed throughout the United States. Of note, only 5% of the general population Cohort 1 was low literacy.

The objective was to evaluate the effectiveness of the label warning “If you need to urinate frequently, it could be an early sign of pregnancy, diabetes, a UTI or more serious condition. If you think you could have one of these conditions, it is important to see a doctor before using this product.” Additionally, the label states “If pregnant or breastfeeding, ask a health professional before use.” Potential respondents were screened over the telephone and then directed to a market research facility. At the site, they reviewed the Oxytrol package labeling and then made a self-selection decision as to whether the product was right for them to use, based on the question “Do you believe that the product is appropriate for you to use right now, or not?” Each respondent was then asked two general open-ended follow up questions: “Why do you say that?” and “What led you to that decision?” “Finally, those who gave a positive self-selection response were asked one additional question which specifically challenged the decision they had made, in order to gain deeper knowledge about their reasoning process or diagnose any misunderstandings on

the part of the respondents.

The self-selection decision was based upon the percentage of respondents who correctly indicated that the Oxytrol product was not appropriate for them to use and/or that they would talk to a doctor first.

Social Science Comments:

*The additional question that challenged the decision made (“challenged” being the Sponsor’s own wording from the final report) was “Earlier, you said that you believe the product is appropriate for you to use right now. However, the warning on the package states that ‘If you need to urinate frequently it could be an early sign of pregnancy.’ It also states ‘If pregnant or breastfeeding, ask a health professional before use’. I would like to explore this issue a little bit more because it will help us improve the information on the label. As best as you can, please tell me more about why you thought it would be okay to use this product even though you are currently pregnant?”*

**B) Key Findings:**

The Sponsor stated that as a result, 12 additional respondents were placed in a mitigated category since they then mentioned talking to a doctor. Additionally, five other subjects then indicated that Oxytrol was not appropriate for them to use or that they were unsure of this, and they were also placed in the mitigated category. As a result of the mitigation of Cohort 1 responses, the point estimate went from 88.3% to 91.6%, with the lower bound going from 84.2% to 87.5%. The low literacy cohort had an initial point estimate of 63%, with a lower bound of 54% score. This was mitigated to 68%.

Social Science Comments:

*The validity of the mitigated results here is questionable since the methodology may have directly coaxed the respondents into changing their answers. However, the proposed package has since been changed to alter the silhouette from a woman in a tent-like dress (which could have implied that this was for pregnant women) to a woman with a narrow waist who is not visibly pregnant. Given that visual icons may help with comprehension, particularly among the less literate, I think that this is a significant improvement.*

**X) Self-Selection in Men with OAB Symptoms (92061) – conducted in late 2009:**

**A) Methodology:**

- Cohort 1 – General population men 18+, n=354
- Cohort 2 – Low literate men 18+, n=217

The objective of this study was to evaluate the self-selection decision on the specific warning “Do not use if you are male” on the OTC Drug Facts Label. The target threshold was set a priori at 90%.

This study utilized an all comers recruitment method in nine consumer research sites, with advertising for anyone suffering from OAB symptoms. No reference was made in the advertising to this being a product for women only. Women who responded were eliminated during the screening process in a masked manner such that it was not apparent as to why they were eliminated. Men were directed to a local research site if they qualified. Subjects were given the OTC Drug Facts label to review in private and to read at their own pace. They were then asked the self-selection question “Do you feel this product is right for you to use?” They were then asked a follow up probe “Why do you say that?” in order to gain insight into the subject’s rationale for his response. Finally, the REALM was administered to screen for health literacy. Unlike in most of the other studies, 16% of the general population cohort here tested as low literate – a relatively high representation of the low literate population.

The self-selection endpoint was the number of respondents in the general population who had a correct overall response, divided by the number of respondents in the general population who answered the question.

## **B) Key Findings:**

90% (LB of 87%) of the general population stated that it was not ok to use. An additional five respondents were then mitigated to be correct based on their open end responses – when these additional participants were taken into account, 92% of men had made a correct decision (LB 88%) This came close to the 90% target threshold for this study.

### *Social Science Comments:*

*There was a more adequate subsample of low literates in the general population (as compared with the other studies in this submission) in addition to the augmented low literacy cohort.*

## **XI) Self-selection/Self diagnosis study in women with OAB symptoms; also four other subpopulations: men, diabetics, those with glaucoma; and those pregnant or nursing (2008-19) – conducted in early 2009:**

### **A) Methodology:**

- Cohort 1 – Normal literacy females 18+ who self reported suffering from urinary symptoms, n=218
- Cohort 2 – Low literacy females 18+ who self reported suffering from urinary symptoms, n=137
- Cohort 3 – Four sub-populations; health literacy was tested and reported:
  - Males, n=172
  - Diabetics, n=42
  - Glaucoma, n=12
  - Pregnant/nursing, n=10

The primary objective of this study was to evaluate the ability of consumers to correctly self-diagnose overactive bladder and self-select the product based on product uses and warnings, based on their personal medical history and the product labeling. A secondary objective of the study was to evaluate incorrect self-selection decisions by risk categories (minimal/insignificant medical risk, possible medical risk, and medical risk)

This study was conducted at eight clinical research sites in the United States. Two were in Florida, and there was one each in Arizona, Arkansas, California, Ohio, Kentucky and North Carolina; none were on the East Coast. Cohorts 1 and 2 were recruited using advertising and community outreach methods in order to reach an all comers population. Cohort 3 (males, pregnant/breastfeeding women, diabetics, glaucoma sufferers) was recruited from site databases, since it was also comprised of those who self reported suffering from urinary symptoms. The recruitment was masked so that the consumers did not know that they were being recruited for a given subpopulation.

Subjects were given an opportunity to read and review the Drug Facts Label of the product and were asked if they thought the product was appropriate for them to use (self-selection). They were then asked for their rationale for the decision. Cohort 3 subjects were discontinued at that point: Cohorts 1 and 2 were asked to sign an informed consent, and then asked if they believed they had overactive bladder (self-diagnosis). They then provided a medical history, medication history, urinalysis and pregnancy test (if applicable). A physician then conducted a physical exam, including a pelvic examination. Subjects were given an option to return for an optional visit 2 within five days if they were not prepared for the pelvic or medical examination. The physician then evaluated, based on all the information available, if the subject had overactive bladder and if the product was appropriate for them to use. The physician decisions were compared against the subjects' decisions. If these decisions did match, a study coordinator conducted a final interview with the patient to understand the rationale for the decision. In the event that the subject had medically significant findings, or pregnancy test results requiring follow up, they were informed of the need to seek medical care and asked to sign an attestation to that effect.

The exclusion criteria for this study were not only inconsistent with the exclusion criteria for the other studies in this NDA submission; they were also inconsistent with standard market research industry practice. Specifically:

- Subjects were excluded if they had participated in another clinical study or received an investigational drug only within the past 30 days. The standard practice is one year.
- Subjects were excluded if they worked for a pharmaceutical, healthcare or market research company. However, they were not excluded if household members worked for these companies.

*Social Science Comments:*

*Standard exclusion criteria are that subjects cannot participate if they have participated in another clinical or marketing research study within the past year, not 30 days. Moreover, standard criteria are that subjects cannot participate if they or anyone in their household is*

*currently employed by the above companies. In this case, the clear potential for “professional respondents” was introduced.*

For the analysis, subjects’ responses to the selection question were compared with the physician recommendation. Correct selection occurred if the physician’s decision and the subject’s decision were in agreement. Also, other responses were considered incorrect and the reasons for those responses were obtained and analyzed. Regarding self-diagnosis, subjects were asked if they had symptoms of overactive bladder. The responses to the diagnosis question were matched to the physician diagnosis. Instances in which the diagnosis response did not match the physician response were considered incorrect.

Below are a priori risk categories for evaluating subjects who incorrectly self-selected:

- Narrow angle glaucoma, pregnant/breastfeeding/ previous allergic reaction to product – 90%
- Urinary retention, gastric retention, male, UTI symptoms, liver or kidney disease, diagnosed diabetes, unexplained weight loss, history of kidney stones, currently using diuretic – 85%
- Currently using an RX medication for OAB – 80%

*Social Science Comments:*

*There was a difference between the n sizes at the start of the study and those at the end, probably due to, among other reasons, that a pelvic exam was required for two of the three cohorts. The n sizes above reflect the number of subjects who completed the study. It is very difficult to analyze the data to determine whether there was a non-response bias that could impact the study findings, particularly without having the individual CRFs provided as part of the submission.*

**B) Key Findings:**

- 89% - 91% self-diagnosed correctly
- There were no differences in demographic or medical profile of those who incorrectly self diagnosed vs. those who correctly self diagnosed.
- There were no suspicious lesions or symptoms consistent with cancers of bladder or vagina.
- Eight subjects did not think they had OAB but the doctor thought they did
- There were four cases of possible undiagnosed urinary retention. In these instances, the subjects made an incorrect self-diagnosis of OAB. There were an additional two cases in which the subjects made a correct self-diagnosis of OAB but were additionally believed to have undiagnosed urinary retention, and therefore were determined to have made an incorrect self-selection.
- There were three cases of possible undiagnosed UTI. In these instances, two of the subjects made an incorrect self-diagnosis of OAB.
- There were an additional six cases of possible UTI based on lab findings only; however, all subjects were asymptomatic and none were over 65. In all cases, the

- physician also confirmed the finding of OAB.
- There were three cases of possible undiagnosed diabetes
  - Of males, 26% incorrectly selected the product.
  - 67% of diabetics incorrectly failed to state that they would consult their doctor prior to use (the label used in this study stated that consumers should ask their doctor before use if they have diabetes)
  - There was one subject who reported unexplained weight loss and incorrectly selected by not stating she would consult the doctor.
  - 50% of glaucoma patients incorrectly selected – but then it turned out that they had open angle and not narrow angle
  - 60% pregnant/nursing subjects incorrectly selected the product
  - 100% (n=3) of gastric retention subjects incorrectly selected the product
  - There were no cases of self reported or physician suspected kidney or liver disease among those who selected product
  - There were no cases of individuals who selected the product and also self reported liver or kidney stones or in which physician suspected they had a history
  - There were no cases of pain or burning while urinating or cloudy urine self reported by individuals who selected the product or cases in which the physician suspected UTI
  - There were no cases in which the consumer self selected and reported that they had seen blood in urine; in five cases, the doctor stated that the subject should not select the product based on blood evidenced in the lab report.
  - There was one case of a subject incorrectly self-selecting while on a prescription medication for OAB.
  - There were no cases of a subject incorrectly self-selecting while on a diuretic.

*Social Science Comments:*

*This study has not been reviewed extensively due to the above validity concerns. The actual use study, which was conducted later, provided more valid and substantial insights as to what happened in a naturalistic setting when individuals with most of the above conditions were presented a real option for using the product. Although pregnant women and men were excluded up front in the actual use study, they were the focus of subsequent targeted self-selection studies which are discussed above.*

**XII) Final Discussion, Conclusions and Recommendations:**

The discussion below summarizes the study results for the key medical issues outlined earlier in this document. I also provide recommendations for enhancement of the proposed label. These recommendations are based upon the consumer research findings discussed in this study only; they do not reflect findings from the actual use study and therefore, I acknowledge that there may be other findings from that study that may reasonably alter what is recommended below. Note: the recommendations are based upon the final proposed label, and not the labeling that was utilized for either the pivotal label comprehension study or any of the other consumer research discussed here.

### **A) Consumer Self-Identification of OAB:**

The label comprehension studies did not conclusively demonstrate that consumers could look at a label and sift through a scenario combining symptom duration and types of symptoms in order to determine that Oxytrol for Women was okay for someone to use. In fact, scenarios involving a two week duration of symptoms scored poorly in studies prior to the pivotal study. It is true, however, that when cued to look at the label as in the pivotal study, people understood that there was a three month minimum duration of symptoms (though less so in the low literate population and elderly populations). For this particular product, adequate comprehension of the minimum duration of symptoms may be sufficient with respect to the overall consumer takeaway since any other undiagnosed conditions may become more apparent within that period of time.

**Social Science Recommendation for Label: *Italicize the “at least” in the ‘Uses’ sentence: You may be suffering from overactive bladder if you have had 2 or more of the following symptom for *at least 3 months.****

**This will further call attention to the minimum length of symptom duration prior to using the product.**

### **B) Urinary Retention:**

Although respondents missed the threshold on these questions and there were differences between low and normal literates, it may be reasonable to assume that if someone has been diagnosed by a doctor with this condition, they would be more attuned to this aspect of labeling. The proposed label has been revised to reflect that fact that people need to have been diagnosed with a doctor for this condition in order for this warning to be relevant for them. Absent this, it's understandable that people looking at the label who are not diagnosed with the condition could have confused urinary retention with OAB.

For further insights, it's important to look at what happened in the actual use study with respect to any recommendations for labeling changes. Therefore, I defer to the medical officer recommendations in his review.

### **C) Gastric Retention:**

As above, although respondents missed the threshold on these questions and there were differences between low and normal literates, it may be reasonable to assume that if someone has been diagnosed with this condition, they would be more attuned to this aspect of the labeling.

For further insights, it's important to look at what happened in the actual use study with respect to any recommendations for labeling changes. Therefore, I defer to the medical officer recommendations in his review.

## D) Diabetes Risk:

The results presented in the pivotal were in some ways “best case” numbers among the at risk population, for the methodological reasons cited in my review. The pivotal (as well as earlier studies) also did not cover all of the symptoms listed on the label. Thus, it has not been conclusively demonstrated that people at risk with some of the symptoms mentioned on the label would have comprehended from the label to check with their doctor first since they may have diabetes.

**Social Science Recommendation: The “Ask a Doctor Before Use If you Have...” section of the proposed label is not as clear as it could be because it mentions risk factors and symptoms in the same sentence but then does not specify which is one and which is the other. I recommend that this be changed to read:**

- **Risk factors for diabetes such as history in your immediate family**
- **Symptoms of undiagnosed diabetes, such as frequent urination together with:**
  - **Excessive thirst**
  - **Extreme hunger**
  - **Increased tiredness**

## E) UTI:

Undiagnosed UTI was not tested in the pivotal (except for foul smelling urine) but labeled symptoms were fully tested in the 65+ LCS, where they tested reasonably well even with the methodological issues there. Keep in mind that the low literacy representation in the 65+survey population was also low, however. Comprehension of UTI symptoms also was tested in the initial LCS but the methodological issues with that survey call its findings somewhat into question.

The Sponsor made some relevant changes to the proposed label from the one that was used in the pivotal study. In the proposed label, the Warnings section has been bulleted to make clearer that frequent urination could be a symptom of UTI (among other conditions).

However, the wording was also changed from “If you think you have one of these conditions, (b) (4)” to “If you think you might have one of these conditions, see your doctor before use”. The proposed label also tweaked the format of the Do Not Use section to make clearer that the symptoms cited were problematic because they could be UTI, and reiterated that a doctor should be seen as soon as possible.

**Social Science Recommendation for Label: Regarding the Warnings section, I think that the newer format is clearer, but I think the earlier version phrase that it is (b) (4), and that the label should be changed back to contain that wording. Although the revised Do Not Use section goes toward making this point, (b) (4) also addresses the other conditions listed in Warnings, whereas these conditions are not discussed in the Do Not Use section. Therefore, I recommend that the text be changed to “If you think you might have one of these conditions, (b) (4)**

## **F) Pregnancy:**

Pregnancy was not addressed in the pivotal survey. With regard to “undiagnosed pregnancy” mimicking OAB symptoms, the 90% threshold was met although the question was a bit leading. Note: the subsequent proposed label bullets “early pregnancy” in the Warnings section and therefore makes it easier to see.

With regard to women who know they are pregnant, a self-selection study was conducted which did not meet the threshold, even with a general population low literacy cohort of just 5% and even with the Sponsor embedding a “challenge” question that potentially led to a lot of respondents rethinking their responses. As for the augmented low literacy cohort, this had a lower bound score of 54%. However, it is important to note that this was with a prior version of the package, in which there was a silhouette of a woman depicted with a unwaisted, loose-fitting dress, thereby perhaps implying that the drug was for pregnant women. The figure on the box has been significantly redrawn to emphasize a slim (e.g., non-pregnant) woman.

**Social Science Recommendation: I defer to the medical officer with respect to any issues that might be relevant for pregnant women; I think that the revised drawing on the label is very beneficial in facilitating appropriate self-selection.**

## **G) Men:**

In the self-selection study for men (which appears to have fewer methodological issues than the other self-selection studies), 90% (lower bound of 87%) of the general population comprehended that the product was not okay to use. There was some upward mitigation but it only raised the resulting score by one percentage point. There also were no significant differences between low and normal literates. In the label comprehension study that involved a small male cohort, 86% LB of men understood that it was not okay for men to use the product.

**Social Science Recommendation: Given the product name, accompanying female figure drawing and pink package coloring, as well as the Do Not Use if male, I think that this is sufficient to convey the appropriate message.**

## **H) Elderly:**

In general, the 65+ population had reasonably well comprehension of the label, with lower bounds generally from 85% and up – although the low literacy representation was low as was geographic representation and so therefore these are potentially “best case” scores. Note, however, that comprehension among the elderly of the three months minimum symptom duration was relatively low, at 74% lower bound. In the pivotal study, there were almost no significant differences with respect to age range.

**Social Science Recommendation: I defer to the Medical Officer.**

**I) Post Advisory Committee Comments:**

- 1. Several members of the Advisory Committee (AC) voiced the belief that OAB is a diagnosis of exclusion and therefore the physician needs to be involved, since lay consumers cannot make this diagnosis by themselves – regardless of whether they understand the label. (Label comprehension did not appear to be a focus of almost any of the discussion). There was concern about the male self-selection study not meeting the target threshold, despite the fact that it was just slightly below threshold. However, it’s not clear that if it had met the 90% threshold that the AC panel members would have felt differently. Although men do use Oxytrol now as an Rx product, their physicians are presumably excluding conditions such as benign prostatic hypertrophy first. Clearly there was concern about even 10% of men interested in using this product without seeing their physician first. This medical concern regarding the validity of the target threshold established by the Sponsor is beyond the scope of the social science review and therefore I defer to the medical officer.**
- 2. Likewise, a panel member mentioned that s/he also disagreed with the diabetes threshold at 85% and believed it should have been higher. Again, this medical concern regarding the validity of the target threshold established by the Sponsor is beyond the scope of the social science review and therefore I defer to the medical officer.**
- 3. Regarding diabetes risk, several of the AC members did not believe that it was necessary to note “family history” as a risk factor on the label and noted that the potential deletion of this item, as well as kidney stones, would free up more space to highlight other more important concerns. I disagree with eliminating family history from the label, because I think that in general the label comprehension studies (including the mitigation to get to the final comprehension scores) showed that the understanding of this as a risk factor was higher than understanding extreme thirst as a symptom – and as I’ve pointed out, the other symptoms weren’t even tested. To the extent then that family history might facilitate label readers to glance at the diabetes section of the label, I am concerned that its elimination may cause people to not even bother to read that section since they might think it doesn’t apply to them.**
- 4. There was also some concern voiced about the pregnancy self-selection study, particularly with regards to low literates. A couple of panel members voiced the belief that the revised icon would not necessarily deter pregnant women from selecting to use the drug (without asking a doctor first). Oxytrol for Women is pregnancy category B. As this is a clinical issue, I defer to the FDA clinical reviewers to address the concerns voiced by some**

of the AC members.

- 5. Although the actual use study was not within my scope of responsibility for this NDA submission, I do wish that the Sponsor had not excluded men and pregnant women up front in this study, since that in a sense would have been a “real world validation” of the self-selection research. I think that data obtained on how many in each group did and did not want to purchase and use the product after reading the label (even if they were subsequently excluded) could have been very helpful in placing the self-selection research in appropriate context.**
- 6. Another major concern of the AC focused on the elderly population. Specific concerns were expressed around setting an age limit for OTC use and addressing the potential for drug-drug interactions in older adults who may be taking a number of drugs. These specific concerns would not have been addressed in label comprehension and/or self-selection with regard to the label that was undergoing testing at the time.**
- 7. Finally, one AC member mentioned that there were other topics of concern that were not covered in any of the research. The example cited was a concern that parents of young children might try to administer this drug to them. Although it was not presented in the meeting due to time constraints, the initial label comprehension study did have a question about whether it was okay to give Oxytrol to an eight year old, and the comprehension was very high, with lower bound scores of 95%, 96% and 98% among NL female OAB sufferers, LL female OAB sufferers and general female non-sufferers, respectively.**

# **APPENDICES**

### xiii) Appendix 1 – Key Pivotal LCS Findings

Metric	Cohort 1 point est n=472	Cohort 1 LB	Cohort 1 UB	Cohort 2 point estimate n=120	Cohort 2 LB	Cohort 2 - UB	NL (point estimate)	LL (point estimate)
Not ok, allergic to oxy	95.1	92.8	96.9	91.7	85.2	95.9	95.9	90.1
Stop use, ask a doctor if allergic	93.2	90.6	95.3	90.8	84.2	95.3	93.0	92.1
Not ok, has urinary retention	91.3	88.4	93.7	84.2	76.4	90.2	92.7	81.6
Not ok, has gastric retention	89.8	86.7	92.4	74.2	65.4	81.7	90.9	74.3
Stop use and ask doctor, red/itchy blisters	88.6	85.3	91.3	89.2	82.2	94.1	88.9	88.2
Not ok, has narrow angle glaucoma	87.7	84.4	90.5	80.0	71.7	86.8	90.2	74.3
Ask a doctor, kidney stones	89.8	86.7	92.4	90.8	84.2	95.3	90.5	88.8
As a doctor. has liver disease	83.9	80.3	87.1	90.0	83.2	94.7	84.5	86.8
Symptoms 3+ months	87.3	83.9	90.2	69.2	60.1	77.3	88.0	71.1
Not ok, stress incontinence	77.3	73.3	81.0	63.3	54.1	71.9	79.5	59.9
Ask a doctor family history of diabetes	88.8	82.8	93.2	na	na		90.8	72.2
Ask a doctor, frequent urination, excessive thirst	88.1%	82.1	92.7				90.1	72.2
Knowledge of specific OAB symptoms	85.6	82.1	88.6	81.7	73.6	88.1	85.9	81.6

## XIV) Appendix 2 - Pivotal LCS Label

7 Page(s) of Draft Labeling have been Withheld in Full as b4  
(CCI/TS) immediately following this page

(b) (4)

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

/s/  
-----

BARBARA R COHEN  
11/15/2012

LESLEYANNE FURLONG  
11/15/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: November 9, 2012

Reviewer(s): James Schlick, RPh, MBA  
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh  
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, Pharm.D., MPH  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Oxytrol for Women (Oxybutynin) Transdermal System  
3.9 mg/day

Application Type/Number: NDA 202211

Applicant: MSD Consumer Care, Inc.

OSE RCM #: 2012-786

\*\*\* This document contains proprietary and confidential information that should not be released to the public. \*\*\*

## Contents

1	INTRODUCTION .....	1
1.1	Product Information .....	1
2	METHODS AND MATERIALS REVIEWED .....	1
2.1	Selection of Medication Error Cases.....	1
2.2	Literature Search .....	2
2.3	Labels and Labeling .....	3
2.4	Previously Completed Reviews .....	3
3	INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT .....	3
3.1	(b) (4) Adhesion .....	3
3.2	Font Color Selection for Text on Clear Patch.....	4
4	CONCLUSIONS.....	4
5	RECOMMENDATIONS.....	4
	APPENDICES .....	7
	Appendix A: Database Description .....	7
	Appendix B: Container Label.....	8
	Appendix C: Carton Labeling .....	9
	Appendix D: Prescription Oxytrol Patch.....	11

## **1 INTRODUCTION**

This review evaluates the proposed container label, carton, and insert labeling for Oxytrol for Women, NDA 202211 for areas of vulnerability that could lead to medication errors.

The proposed OTC transdermal product, Oxytrol for Women (Oxybutynin), is a partial Rx to over-the-counter (OTC) switch of the currently marketed transdermal prescription product Oxytrol (Oxybutynin). The proposed switch is for the target population of women, aged 18 and over. The use of Oxytrol by males will remain a prescription indication.

Oxytrol has only one indication: the treatment of overactive bladder. Oxytrol was approved by the FDA in February 2003.

The Applicant proposes to use feminine graphics and colors in the packaging as well as the name modifier, “For Women”, to help differentiate the prescription product from the OTC product. The Applicant also intends to use the same patch for the OTC product that is used for the prescription product.

### **1.1 PRODUCT INFORMATION**

The following product information is provided in the March 26, 2012 proprietary name submission.

- Active Ingredient: Oxybutynin
- Indication of Use: Nonprescription treatment of overactive bladder in women
- Route of Administration: Transdermal
- Dosage Form: Matrix-type transdermal patch
- Strength: 3.9 mg/day
- Dose and Frequency: Apply one patch and wear it for four consecutive days. After 4 days, remove the used patch and apply a new one.
- How Supplied: In cartons containing 4, 10, and 14 patches.
- Storage: Store between 20°C to 25°C (68°F to 77°F).
- Container and Closure Systems: Individual sealed pouch

## **2 METHODS AND MATERIALS REVIEWED**

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Oxytrol medication error reports. We also reviewed the Oxytrol for Women labels and labeling submitted by the Applicant.

### **2.1 SELECTION OF MEDICATION ERROR CASES**

We searched the FAERS database using the strategy listed in Table 1. The beginning date used for the search was April 24, 2012 since the last AERS search conducted for Oxytrol was April 23, 2012 in OSE Review 2012-785.

<b>Table 1: FAERS Search Strategy</b>	
Date	April 24, 2012 to August 24, 2012
Drug Names	Active Ingredient: Oxybutynin Trade Name: Oxytrol Verbatim Term: Oxybut* and Oxyt*
MedDRA Search Strategy	Medication Errors (HLGT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Quality Issues (NEC) (HLT)

The FAERS search identified 6 reports. Each report was reviewed for relevancy and duplication. After individual review, 6 reports were not included in the final analysis for the following reasons:

- Cases not related to the Oxytrol transdermal dosage form that included taking expired medication and doses missed due to the patient forgetting to take the medication.
- Medication error not related to oxybutynin
- Foreign case with wrong dose and no cause stated

## 2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on September 17, 2012 for additional cases and actions concerning Oxytrol. The PubMed search included the search terms “Oxytrol” and “medication error”. The ISMP search included the search terms “Oxytrol”. The following ISMP Newsletters were searched:

- ISMP Acute Care Newsletter
- ISMP Community Edition
- ISMP Nursing Edition
- ISMP Canada Safety Bulletin

The August 24, 2004 edition of ISMP Acute Care Newsletter revealed that confusion between Oxytrol and Uroxatral occurred<sup>1</sup>. Both medications are used to treat overactive bladder. AERS cases (n=2) documenting name confusion between Oxytrol and Uroxatral were discussed in OSE Review # 2010-1491. One case described the potential for confusion between the names Uroxatral and Oxytrol. The second case described confusion between the two names during a verbal discussion of a discharge treatment plan.

---

<sup>1</sup> Institute for Safe Medication Practices. Acute Care Newsletter. August 24, 2004. Volume 9, Issue 17, pg. 3.

### 2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted March 26, 2012 (Appendix B)
- Carton Labeling submitted March 26, 2012 (Appendix C)

### 2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed the labels and labeling for Oxytrol for Women in OSE Review 2010-1491 during the IND phase of development. However, the recommendations in this review were not sent to the Applicant. We will incorporate the comments from the previous review into the current review.

## 3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

### 3.1 (b) (4) ADHESION

During the review of the product, ONDQA alerted DMEPA that particular patches of the prescription patch, Oxytrol, had (b) (4) issues. (b) (4) of the patch creates stickiness around the edges of the patch making the patch stick to the inside of the pouch. This, in turn, can make the patch more difficult to remove from the pouch. ONDQA also noted (b) (4) adhesion issues did not occur until approximately (b) (4) in the lots that were tested by the FDA.

Because the OTC patch is the same patch as the prescription patch, DMEPA requested Oxytrol product quality related reports or complaints from the Applicant pertaining to difficulty removing the system from the container closure (pouch), excessive (b) (4), and adhesion problems. The Applicant reported that 4,282 complaints were documented over 9 years. The Applicant also reported that (b) (4) were distributed during that time and the adhesive complaint rate is (b) (4). DMEPA notes that a complaint case may involve a complaint regarding multiple individual patches. Therefore, multiple patches, each with its own (b) (4) adhesion issue, may only be counted as one case by the Applicant. Additionally, not all complaints regarding adhesive issues are reported. Therefore, the complaint rate is likely higher than the Applicant's reported rate.

ONDQA requested that the Applicant perform additional testing to assess the extent of the (b) (4) quality issue. The Applicant responded with additional data on August 31, 2012. After review of the data, ONDQA maintained that the data did not support an expiration date of (b) (4). The Oxytrol for Women review team met with the Division of Reproductive and Urologic Products (the responsible OND Division for the prescription Oxytrol product) to discuss the data on October 23, 2012. Based on the discussion of the (b) (4) data and the

---

<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI: 2004.

product quality complaints, the team agreed that the proposed expiration date should be shortened to two years. We will monitor for these events post approval.

### **3.2 FONT COLOR SELECTION FOR TEXT ON CLEAR PATCH**

The proposed patch currently contains the product name and strength on the backing membrane. However, the color of the text on the clear backing layer lacks visibility, particularly if a patch detaches and falls to the floor. A more visible color for the text on the backing membrane will make the more patch more visible lying on the floor. This will make it more likely that the patch is noticed on the floor and picked up before a young child places the fallen patch on their skin. Post-marketing data has shown that young children have picked up patches from the floor and either placed the patch on their own skin or swallowed the patch leading to serious adverse events and death. Specifically, this has occurred with Fentanyl patches in the past.

## **4 CONCLUSIONS**

DMEPA concludes that the proposed labels can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. Additionally, DMEPA concludes that the color of the text on the backing membrane for the name and strength of the drug is not clearly visible if the patch is on the floor. With respect to the label, DMEPA recommends changes in the font; relocation of the female graphic, established name, dosage form, and strength; and the inclusion of a calendar to track application days. DMEPA also recommends a post marketing commitment be established for the company to change the color of the text on the membrane backing. Lastly, we recommend that the Applicant provide a semi-annual summary report for product quality related reports or complaints pertaining to difficulty removing the system from the container closure, excessive (b) (4) and adhesion problems.

## **5 RECOMMENDATIONS**

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

- A. General Comments to the Division
  1. The patch contains text identifying the name and strength on the clear backing layer that is a light color. Because of the light text color, the patch may not be easily identified, particularly if a patch detaches and it falls to the floor. To minimize the risk of children picking up the patch from the floor and placing it on their own skin or swallowing, DMEPA recommends changing the text color to a more visible color. Therefore, we would like to get an agreement with the Applicant on a post-marketing commitment (PMC) to:
    - 1) Include a more visible text font color on the backing layer of the drug product that makes the patches more visible if the product detaches and falls to the floor.
    - 2) Fulfill this post-marketing commitment within one year from the date of approval.

2. Because of (b) (4) issues and adhesion problems noted during the review of the product, DMEPA would like to get an agreement with the Applicant on a PMC to monitor these issues. Specifically, DMEPA requests the Applicant provide a semi-annual summary report for product quality related reports or complaints pertaining to difficulty removing the system from the container closure (pouch), excessive (b) (4) and adhesion problems.

B. Container Label and Carton Labeling

1. Present the entire proprietary name “Oxytrol for Women” in the same font, for consistency and clarity. Currently, “for Women” is presented in a smaller, thinner font than “Oxytrol”, and may be overlooked. Since this product is only intended for women and the entire proprietary name is “Oxytrol for Women” it is important that the entire name be presented in a consistent manner to reinforce the entire name as well as the patient population.
2. Relocate the female graphic located directly in front the proprietary name. As currently presented, it interferes with the proprietary name and may be misinterpreted as part of the name. The graphic may be misinterpreted as the letter ‘p’.
3. Per 21 CFR 201.61(c), the regulations governing the statement of identity for OTC drug products (consisting of established name followed by the pharmacologic category) "shall be in a size reasonably related to the most prominent printed matter" on the principal display panel (PDP). We find that the size of the statement of identity (containing the established name of the drug) is not in a size reasonably related to the most prominent printed matter", in this case Oxytrol. Therefore, we recommend an increase in the size of the statement of identity.
4. Increase the prominence of the established name, dosage form, and strength by using a heavier, darker font. As currently presented, this information is difficult to read. Additionally, revise from uppercase to title case to improve readability.
5. On the 4 count and 14 count cartons, ensure the flag that states “New” located in the upper left hand corner of the principal display panel remains on the labeling for no more than 6 months after the initial product launch.
6. Consider adding instructions on what to do if the patch falls off in the Directions section. Language similar to the information provided in the Information for the Patient section of the Oxytrol insert labeling section can be used.
7. Revise the statement of product strength, 3.9MG/DAY, to read 3.9 mg/day so that there is a space between the number 9 and the letter “m”.

C. Carton Labeling

1. If this package is not child resistant, ensure the product complies with the Consumer Product Safety Commission's (CPSC's) regulations on poison prevention packaging. It is required that the statement “Package not child resistant” be on the PDP per 16 CFR 1700.5 (Noncomplying Package Requirements). We recommend that the statement “Keep out of reach of

children” statement be positioned together with “Package not child resistant” statement on the PDP to increase the prominence of the non-child resistant feature.

If you have questions or need clarifications, please contact Ermias Zerislassie, OSE project manager, at 301-796-0097.

## APPENDICES

### APPENDIX A: DATABASE DESCRIPTION

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

4 Page(s) of Draft Labeling have been Withheld in Full  
as b4 (CCI/TS) immediately following this page

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

/s/  
-----

JAMES H SCHLICK  
11/08/2012

TODD D BRIDGES  
11/08/2012

KELLIE A TAYLOR  
11/13/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

CLINICAL INSPECTION SUMMARY

DATE: November 2, 2012

TO: Do Phong, Regulatory Project Manager  
Ryan Raffaelli, Medical Officer  
Leslie Furlong, DNCE Team Leader

FROM: Sharon Gershon, Pharm.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D..  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Susan Thompson, M.D  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202211

APPLICANT: Merck Consumer Care, Inc.

DRUG: Oxybutynin (Oxytrol<sup>®</sup> for Women Patch)

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Relief of overactive bladder symptoms

CONSULTATION REQUEST DATE: April 20, 2012

ADVISORY COMMITTEE: November 9, 2012

INSPECTION SUMMARY REQUEST DATE: End of September, 2012

DIVISION ACTION GOAL DATE: January 25, 2013

PDUFA DATE: January 26, 2013

PROTOCOL: No. CL2008-13: An Oxytrol Transdermal System Actual Use Study (Consumer Trial of Oxytrol, CONTROL)

## I. BACKGROUND:

Merck Consumer Care, Inc. seeks approval to change the marketing status of Oxytrol (oxybutynin) transdermal system from prescription to over-the-counter (OTC) status. The OTC product is proposed for women ages 18 years of age and older for the relief of overactive bladder symptoms. Overactive bladder (OAB) is a syndrome characterized by a collection of symptoms including urinary frequency, urgency, and urge incontinence. An estimated 17% of women in the United States, just over 20 million, suffer from OAB symptoms. It is one of the most common chronic ailments suffered by women, second only to arthritis.

A total of 26 pharmacies from ten communities within the U.S. were used as participating sites to enroll subjects, and to assess consumer use behavior of Oxytrol® for Women in a simulated over-the-counter (OTC) setting. The Protocol No. CL2008-13 entitled “An Oxytrol Transdermal System Actual Use Study (Consumer Trial of Oxytrol), CONTROL was an open-label, single-arm, multicenter, actual use study (AUS).

The study consisted of 4 phases: (1) an initial recruitment screening, (2) an onsite enrollment eligibility interview, (3) a 12-week actual use phase, and (4) an end-of-study follow-up interview at Week 15. A sufficient number of demographically diverse women were targeted for enrollment ( $N \geq 1000$ ) to obtain at least 531 verified users. The primary endpoint was the proportion of verified users who did not stop use when they developed a new symptom referred to in the labeling.

Three pharmacy sites (10, 12, 24) and the CRO (b) (4) were selected for inspection. The three pharmacy sites had the highest number of enrollees. Also, Sites 10 and 12 had the highest number of discontinuations, and Site 12 reported the highest number of serious adverse events. (b) (4) had primary responsibility for all aspects of the study, including protocol development, site selection, data entry, data management and analysis, collection of adverse events, site monitoring, and other such administrative functions.

## II. RESULTS (by Site):

Name of Clinical Investigator/CRO	Protocol No. Site No. No. of Subjects	Inspection Date	Final Classification
Deanne Jungbluth, Pharm.D. Stevenson Family Pharmacy 6201 King Hill Ave. St. Joseph, Mo 64504	Protocol CL2008-13 Site #10  56 subjects	July 16-20, 2012	Preliminary NAI (EIR pending)
Charles Mallinson Matt's Medicine Shoppe 11200 ½ E. U.S. Highway 24 Independence, MO 64054	Protocol CL2008-13 Site #12  52 subjects	July 23-27, 2012	VAI
Neil Leikach Catonsville Pharmacy 6350 Frederick Rd. Baltimore, MD 21228	Protocol CL2008-13 Site #24  26 subjects	June 25-27, 2012	NAI
(b) (4)			

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Pharmacy Site #10:** Deanne Jungbluth, Pharm.D., Stevenson Family Pharmacy  
6201 King Hill Ave., St. Joseph, MO 64504-2063

a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. Deanne Jungbluth has one IND in CDER's COMIS database, and no prior inspections. At this site, 133 subjects began the screening process and 56 subjects enrolled (purchased study medication). Eight subjects withdrew, and 48 subjects completed the study. The pharmacy primarily performed the functions of obtaining signed informed consent (IC), providing study medication, and performing the 12-week urinalysis test, as required by the protocol. The FDA field investigator reviewed IC documents for all 56 subjects. An additional number of subject charts were chosen to verify adherence to the protocol, 12-week urinalysis, and distribution of study medication.

b. **General observations/commentary:** The inspection was classified as NAI. No

objectionable conditions were found, and no Form FDA-483 was issued.

- c. **Assessment of data integrity:** No significant regulatory violations were noted. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication

**PLEASE NOTE: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator, An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

2. **Pharmacy Site #12:** Charles Mallinson, R.Ph., Matt's Medicine Store  
11200 ½ E. U.S. Highway 24  
Independence, MO 64054

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program (CP) 7348.811. Charles Mallinson has one IND in the CDER COMIS database and no prior inspections. At this site, 59 subjects were screened, 52 subjects enrolled (purchased study medication), and 43 subjects completed the study. There were no deaths that occurred during the study at this site. The pharmacy primarily performed the functions of obtaining signed IC, providing study medication to subjects, and performing the 12-week urinalysis test. These functions were outlined in the protocol. A total of 52 subject records were reviewed for IC procedures, and 26 subject records were reviewed for adherence to the study protocol.
- b. **General observations/commentary:** Deficiencies in the IC process and failure to follow the investigational plan were noted on a 2-observational item Form FDA-483. Dr. Mallinson sent a response letter dated April 9, 2012. OSI considers his response acceptable. The citations were as follows:

1) Failure to obtain IC in accordance with 21 CFR Part 50 from each subject prior to conducting study-related tests. Specifically, the site failed to re-consent nine subjects with a later version of the Informed Consent Document (ICD) when they returned to the pharmacy at a later visit.

*OSI Reviewer Comments: The sponsor was aware of this situation and the IRB was notified at the end of the study. The changes to the ICD related to subjects returning to the pharmacy at Week 12 so the pharmacist could conduct a urinalysis test. Based on results of the urinalysis test, subjects might be instructed to see a physician. The Review Division is aware of many subjects throughout the study who did not comply with this latter amendment to the protocol. This finding is most likely not significant in terms of overall safety to subjects, but the Review Division should evaluate.*

2) An investigation was not conducted according to the investigational plan. Specifically: a) the 12-week urinalysis was not performed for 13 of 52 subjects; and b) for 27 subjects, the site used urinalysis test strips that had failed QC testing for nitrite, glucose, and leukocytes.

*OSI Reviewer Comments: When Quality Control (QC) testing was performed on the test strips for urinalyses on 8/3/10, the glucose reading was greater than 2000 mg/dL, which is outside the reference range of 100-1000 mg/dL. These strips which failed QC were used in the study until 2/16/11. When QC was performed on urinalysis test strips on 2/6/11, the nitrate and leukocyte values were not found to be negative. The defective strips were used until 3/4/11. It is unlikely that the values were significantly outside the acceptable range and so did not pose a significant safety risk to subjects. This issue is probably more of a site quality issue, versus a safety issue.*

- c. **Assessment of data integrity:** The Review Division is aware that many subjects did not return to the pharmacy for a urinalysis at Week 12, and can decide if this poses a safety risk to subjects in this study. The other observational findings appear minor and unlikely to significantly impact the results of this study. OSI recommends the data from this site acceptable in support of this NDA.

**3. Pharmacy Site 24:** Neil Leikach, R.Ph., Catonsville Pharmacy  
6350 Frederick Road, Baltimore, MD 21228

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program (CP) 7348.811. Neil Leikach has one IND in CDER's COMIS database, and no prior inspections. The study was conducted between May 28, 2010 and January 28, 2011. A total of 150 subjects were screened (by a nurse at (b)(4)), 29 subjects signed IC, there were 3 screen failures, and 26 subjects enrolled (purchased study medication). Seven subjects completed the entire 15-week study, nine subjects discontinued due to adverse events (see below), eight subjects withdrew for various other reasons, and five subjects were lost to follow-up. Complete study records for 26 enrolled subjects were reviewed for correct IC procedures and adherence to the study protocol.
- b. **General observations/commentary:** As per protocol, no paper records were kept for study visits at this site. Mr. Leikach entered all data directly into the 21 Part 11-compliant DATATRAK e-CRF system. All follow-up interviews were done by phone by (b)(4) nurses, who asked questions (as per script) and recorded post-selection behaviors and any adverse events (AEs). All 29 records contained adequate documentation that IC was properly obtained, that subjects met eligibility criteria for enrollment, and that they were properly followed throughout the study conduct. Key data points found in the study records were compared to the data line listings, including primary endpoints, baseline and demographic data, date of test article purchase, visit dates, and other study procedures. No discrepancies were noted. Protocol deviations, AEs and serious

adverse events (AEs) events were found appropriately reported to the sponsor and IRB. The field investigator reported that IRB approvals were appropriately obtained. All subject records and test article accountability records were complete.

There were seven reported AEs and two Serious Adverse Events (SAEs). The AEs were: itching, urinary retention, rash, skin irritation (two), nausea, and constipation. The two SAEs were: Subject 24-0092 had a prior diagnosis of HIV, reported various infections throughout the study and died due to viral pneumonia. Subject 24-0037 was hospitalized due to syncope related to a prior history of drug abuse. All AEs and SAEs were reported to the Sponsor and IRB. No regulatory violations were noted and no Form FDA 483 was issued.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and OSI recommends the data from this site acceptable in support of this NDA.

**4. CRO Inspection:** (b) (4)

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program (CP) 7348.8.09. This inspection was issued to determine validity of data of subjects enrolled by the pharmacy sites and to determine the adherence to the regulations applicable to CROs.

The inspection focused on the following clinical investigator sites: Site #10 (Stevenson Family Pharmacy), Site #12 (Matt's Medicine Store), and Site #24 (Catonsville Pharmacy). During the trial, subjects reported AEs events during phone interviews conducted by (b) (4) nurses at Weeks 3, 7, 12 and 15. Subjects also maintained a diary where they documented AEs and submitted to (b) (4). (b) (4) was responsible for reporting AEs to the Sponsor and IRB.

The inspection reviewed the following: monitoring reports and regulatory documents for the three sites above; SOPs for selection of monitors and monitoring procedures, SOPs for site initiation, interim monitoring and site close out visits, SOPs for site recruitment and qualifications for designating principal investigators; procedures for data collection; procedures for DATATRAK validation; test article accountability records; document and record retention; IRB approvals and continuing review; and staff training programs.

The FDA field investigator reviewed a sampling of subject files for Site #10 and Site #24. Site subject records for Site #12 were off-site for an FDA inspection and unavailable during this inspection. The review included phone interviews conducted by (b) (4) nurses, patient use diaries, and Informed Consent Documents. There was a comparison of eCRFs with data listings provided by the sponsor. The FDA field investigator reviewed the electronic data capture (EDC) application managed by DATATRAK, including access privileges, training, data query process and resolution.

The FDA field investigator reviewed AEs at Sites #10, 12 and 24.

- b. **General observations/commentary:** A total of ten serious adverse events (SAEs) were reported from these three sites during the trial. All SAEs were reported to the Sponsor and IRB.

In general, the FDA field investigator found no significant observations of noncompliance, and no Form FDA 483 was issued. Two minor protocol deviations were discussed: Subject 24-0122 with glaucoma was enrolled despite exclusion criteria of ‘narrow angle glaucoma’, and Subject 10-0102 was not contacted at Week 7, as required by the protocol. These were isolated occurrences.

- c. **Assessment of data integrity:** The CRO had adequate oversight of the study, and OSI recommends the data submitted by the CRO may be used in support of the respective indication

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three pharmacy sites and the CRO were inspected in support of NDA 202211. No regulatory violations were found during the inspections at two pharmacy sites (Site #10, Deanne Jungbluth, St. Joseph, MO and Site #24, Neil Leikach, Baltimore, MD), and no Form FDA-483 was issued. Results of the inspection of the CRO (b) (4) indicate that (b) (4) had adequate oversight of the study, had adequate site monitoring, and that all data from the sites correlated to data the sponsor submitted to FDA. The inspection of Matt’s Medicine Shoppe (Site #12, Charles Mallinson) was classified as VAI, and a two-observational Form FDA-483 was issued for the failure to obtain IC according to procedures outlined in 21 CFR Part 50, and failure to follow the investigational plan. Although regulatory violations were noted at Site #12, they are unlikely to significantly impact primary safety and efficacy analyses for NDA 202211. The data from the sites and the CRO submitted in support of NDA 202211 may be considered reliable in support of the NDA.

**PLEASE NOTE: The EIR was not available at the time this CIS was written for Site 10. The observations noted are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

{See appended electronic signature page}

Sharon K. Gershon, Pharm.D.  
GCPAB Reviewer  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

{See appended electronic signature page}

Susan D. Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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

/s/  
-----

SHARON K GERSHON  
11/02/2012

SUSAN LEIBENHAUT  
11/02/2012

SUSAN D THOMPSON  
11/02/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Drug Use Review**

Date: October 10, 2012

Reviewer(s): Patty Greene, Pharm.D., Drug Use Data Analyst  
Division of Epidemiology II (DEPI II)  
Elizabeth Kang, MPH, Operations Research Analyst  
Division of Epidemiology I (DEPI I)

Team Leader Grace Chai, Pharm.D.  
Division of Epidemiology II  
Esther Zhou, MD, PhD  
Division of Epidemiology I

Director Judy A. Staffa, Ph.D., R.Ph.  
Division Director, Division of Epidemiology II  
Tarek Hammad, MD, PhD, MSc, MS  
Deputy Director, Division of Epidemiology I

Subject: Oxytrol Drug Utilization Review

Drug Name(s): Oxytrol (oxybutynin patch)

Application Type/Number: NDA 21-351

Applicant/sponsor: Watson Pharma, Inc.

OSE RCM #: 2012-1208

**\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\***

## CONTENTS

EXECUTIVE SUMMARY .....	2
1 INTRODUCTION.....	2
1.1 Background .....	3
1.2 Product Labeling .....	3
2 METHODS and MATERIALS .....	3
2.1 Determining Setting of Care .....	3
2.2 Data Sources Used .....	3
2.3 Duration of Use .....	4
3 RESULTS.....	5
3.1 Outpatient Dispensed Prescriptions for Oxytrol by Patient Age.....	5
3.2 Patient Utilization of Oxytrol by Patient Age .....	5
3.3 Duration of Use for Oxytrol by Patient Age and Gender.....	6
4 DISCUSSION.....	7
5 CONCLUSIONS .....	8
6 APPENDICES.....	9
6.1 APPENDIX 1: Tables and Figures.....	9
6.2 APPENDIX 2: Drug Use Database Descriptions.....	13

## EXECUTIVE SUMMARY

This review examines drug utilization for Oxytrol (oxybutynin patch) in the adult population stratified by age (0-64, 65+ years). To assess the extent of Oxytrol use and the duration of treatment, we examined nationally estimated prescription and patient data to determine exposure by patient age and duration of use in the U.S. outpatient retail pharmacy setting from years 2003 through 2011.

- Approximately 2.2 million prescriptions for Oxytrol were dispensed and approximately 481,000 patients received a dispensed prescription in the outpatient retail pharmacy setting from years 2003 through 2011.
- The annual number of prescriptions dispensed for Oxytrol decreased by 78% from a peak in use of nearly 422,000 prescriptions in year 2004 to 92,000 prescriptions in year 2011.
- The annual number of patients who received dispensed prescriptions of Oxytrol also decreased by 86% from 161,500 patients in year 2004 to approximately 23,000 patients in year 2011.
- Using patient-level claims data (IMS Data Extract Tool), we found that 82.5% of Oxytrol users were female (N=190,287), of which 75% had 1 to 2 treatment episodes during the study period 2003 – 2011. The mean and median duration of episode per female patient were about two months and one month, respectively. While the range of duration varied, about 75% of patients had episodes that lasted about  $\leq 2$  months, and only 1% of patients had episodes that lasted longer than one year.
- Over the 9-year study period, about 75% of patients had total treatment not exceeding five months, and only about 1% of patients had extremely long total treatment duration that lasted longer than 3.5 years. The mean ( $\pm$ SD) cumulative (total) treatment duration was 142 ( $\pm$ 253) and 152 ( $\pm$ 251) days for female patients under 65 years of age and patients 65+ years of age, respectively. Median total treatment duration was about two months. Again, the range of total treatment duration varied.

## 1 INTRODUCTION

The Division of Nonprescription Clinical Evaluation (DNCE) is evaluating a proposed prescription to over-the-counter switch of Oxytrol (oxybutynin patch). Oxytrol patch is indicated for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency. In the approval process, a drug product applied to the skin with the potential to be used *chronically* is typically supported by chronic toxicity and carcinogenicity data.<sup>1</sup> To help assess the requirement for dermal carcinogenicity data from the Sponsor, the Division of Epidemiology II (DEPI II) provides an analysis of

---

<sup>1</sup> Li, Xinguang Pharmacology/Toxicology Filing Checklist for NDA/BLA or Supplement May 2012

Oxytrol patient exposure and duration of use in U.S. outpatient retail pharmacies from years 2003 through 2011.

## 1.1 BACKGROUND

On March 26, 2012, Merck Consumer Care, Inc. submitted an NDA application for *Oxytrol for Women* (oxybutynin transdermal system) and requested to change the marketing status of the product from prescription to nonprescription. Oxytrol for Women is indicated for the relief of overactive bladder symptoms for women 18 years and older. Based on an initial overview of the NDA application filing, a drug product applied to the skin with the potential to be used *chronically* is typically supported by chronic toxicity and carcinogenicity data.<sup>2</sup> As of the filing date, a dermal carcinogenicity study was not conducted for the oxybutynin transdermal system. To help assess if the Agency should request the Sponsor to fulfill the requirement for dermal carcinogenicity data, the Division of Epidemiology II (DEPI II) has been requested to provide an analysis of Oxytrol patient exposure and duration of use in U.S. outpatient retail pharmacies from years 2003 through 2011.

## 1.2 PRODUCT LABELING

Oxytrol (oxybutynin patch) is a muscarinic antagonist approved for marketing on February 26, 2003, under NDA 21-351, for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.<sup>3</sup> The dosing for Oxytrol is one patch applied twice weekly (every 3 to 4 days).

NDC 52544-920-08 Box of 8 Systems

## 2 METHODS AND MATERIALS

Proprietary drug use databases were used to conduct this analysis (see Appendix 2 for full data descriptions).

### 2.1 DETERMINING SETTING OF CARE

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for Oxytrol. Sales data for year 2011 indicated that approximately 51% of packages (Eaches) were distributed to outpatient retail pharmacies; 28% were to mail order pharmacies; and 21% were to non-retail settings.<sup>4</sup> As a result, outpatient retail pharmacy utilization patterns were examined. Neither mail order nor non-retail settings data were included in this analysis.

### 2.2 DATA SOURCES USED

---

<sup>2</sup> Li, Xinguang Pharmacology/Toxicology Filing Checklist for NDA/BLA or Supplement May 2012

<sup>3</sup> Oxytrol label Accessed in August 2012. Available at: <http://www.oxytrol.com/>

<sup>4</sup> IMS Health, IMS National Sales Perspectives™. Year 2011. Extracted August 2012. File: NSPC 2012-1208 oxytrol sales 8-27-12.xls

IMS, Vector One®: National (VONA) was used to determine estimates of the number of outpatient dispensed prescriptions for Oxytrol, stratified by age (0-64, 65+ years), from years 2003 through 2011. IMS, Vector One®: Total Patient Tracker (TPT) was used to obtain estimates of the number of patients receiving a dispensed prescription for Oxytrol, stratified by age (0-64, 65+ years), in the outpatient retail setting from years 2003 through 2011.

IMS, Vector One®: Data Extract Tool (DET) was used to determine duration of use for Oxytrol from years 2003 through 2011. DET is a population based dataset containing prescriptions dispensed from approximately 54,000 U.S. retail pharmacies, accounting for approximately 50% of the prescriptions dispensed in the U.S. Prescription records are linked to a unique patient identifier, allowing each prescription to be associated with a unique patient as they receive prescriptions from different pharmacies.

### 2.3 DURATION OF USE

#### STUDY POPULATION

Patients who had at least one prescription claim in IMS DET dataset for an Oxytrol patch between January 1, 2003 and December 31, 2011 were included in the study. To maximize data validity in our analysis, we excluded patients with no recorded age or gender. We further excluded patients if any single prescription claim had missing information on the days' supply or had extreme values.

In total, we excluded 1.3% of patients, including 0.5% of patients with missing gender, 0.02% of patients with invalid age, 0.7% of patients with missing information for days' supply or < 7 days' supply, and 0.1% of patients with more than 100 days' supply in one prescription. We assumed that < 7 days' supply represented a coding error. The 100-day cut-off was used since many health insurance companies do not cover the cost of prescriptions that exceed 100 days' supply. Note these patients (%) are not mutually exclusive; some patients may have had more than one exclusion criteria.

#### MEASURES

Demographic characteristics, including patient age and gender were examined. We estimated the duration of treatment of Oxytrol prescriptions based on prescription dispensing dates and the days' supply. We describe duration of treatment by using treatment episodes per patient and cumulative treatment duration per patient. We also report the duration of the longest episode.

Each treatment episode started on the date of the first dispensing and continued until a treatment gap of >25% of the prior prescription days' supply, or the end of study period. Gaps ≤ 25% were ignored such that the surrounding dispensings were counted as one episode. To estimate the duration of episodes, the date of the first dispensing in a particular episode was subtracted from the end date of the treatment episode.

$$DURATION\ OF\ EPISODE = (last\ prescription\ date + days'\ supply) - first\ prescription\ date$$

Cumulative treatment duration per patient was defined as the sum of all treatment episodes for each patient during the 9-year study period.

### 3 RESULTS

#### 3.1 OUTPATIENT DISPENSED PRESCRIPTIONS FOR OXYTROL BY PATIENT AGE

*Figure 1 and Table 1 in Appendix 1* show the nationally estimated number of dispensed prescriptions for Oxytrol by patient age (0-64, 65+ years) from U.S. outpatient retail pharmacies, years 2003 through 2011. During the examined time, approximately 2.2 million prescriptions were dispensed for Oxytrol. Upon approval in February 2003, the annual number of dispensed prescriptions for Oxytrol increased 3-fold from 122,000 prescriptions in year 2003 to a peak of 422,000 prescriptions dispensed in year 2004. However from year 2004 to 2011, dispensed prescriptions of Oxytrol decreased by 78% from approximately 422,000 prescriptions in year 2004 to 92,000 prescriptions in year 2011.

Oxytrol prescriptions dispensed to elderly patients 65+ years of age accounted for 62% of prescriptions (1.36 million prescriptions) for the entire review period. The proportion of dispensed prescriptions by patient age for elderly patients increased accounting for 56% (69,000 prescriptions) in year 2003 to 62% (approximately 57,000 prescriptions) in year 2011.

Oxytrol prescriptions dispensed to patients under 65 years of age accounted for 38% of prescriptions (820,000 prescriptions) for the entire review period. The proportion of dispensed prescriptions by patient age for patients under 65 years of age decreased accounting for 43% (52,000 prescriptions) in year 2003 to 38% (approximately 35,000 prescriptions) in year 2011.

#### 3.2 PATIENT UTILIZATION OF OXYTROL BY PATIENT AGE

*Table 2 in Appendix 1* shows the nationally estimated number of patients who received prescriptions dispensed for Oxytrol by patient age (0-64, 65+ years) from U.S. outpatient retail pharmacies, years 2003 through 2011. In terms of unique patients, the annual number of patients for Oxytrol more than doubled between years 2003 to 2004 (from 69,000 to approximately 161,000 patients). However from year 2004 to 2011, the annual number of patients of Oxytrol decreased by 86% from approximately 161,500 patients in year 2004 to 23,000 patients in year 2011.

Oxytrol dispensed to elderly patients 65+ years of age accounted for 59% of patients (285,000 patients) for the entire review period. The proportion of elderly patients, by patient age, increased accounting for 53% (approximately 37,000 patients) in year 2003 to 63% (approximately 14,000 patients) in year 2011.

Oxytrol dispensed to patients under 65 years of age accounted for 42% of patients (200,000 patients) for the entire review period. The proportion of patients by patient age who were under 65 years of age decreased accounting for 47% (32,500 patients) in year 2003 to 38% (approximately 8,700 patients) in year 2011.

### 3.3 DURATION OF USE FOR OXYTROL BY PATIENT AGE AND GENDER

#### PATIENT CHARACTERISTICS

A total of 230,623 patients who met the inclusion criteria and had a claim for Oxytrol were identified between 2003 and 2011. Patient characteristics of the study population are shown in *Table 3 in Appendix 1*. Approximately 82.5% of all Oxytrol users were female (N=190,287); 57% of female patients, and 70% of male patients were 65 years or older at the first dispensing of Oxytrol during the study period.

#### DURATION OF USE

*Table 4 in Appendix 1* shows estimates for duration of use.

For females, the mean ( $\pm$ SD) number of prescriptions dispensed per patient during the study period was 4.5 ( $\pm$ 8) for younger patients under 65 years of age, and 4.8 ( $\pm$ 8) for elderly patients 65+ years of age with median of 2.

The mean ( $\pm$ SD) number of treatment episodes per patient was 2 ( $\pm$ 3) with a median (inter quartile range) of 1 (1, 2) episode per patient for both younger and elderly Oxytrol female users. There were 63% of younger patients and 60% of elderly patients who had only one treatment episode during the study period. The mean ( $\pm$ SD) duration of episode per patient was 60 ( $\pm$ 78) days for younger patients and 63 ( $\pm$ 79) days for elderly patients. Median duration (interquartile range) was 30 days (28, 61) for younger patients and 30 days (28, 70) for elderly patients. The distribution was widely spread out; the majority of patients (98%) had a mean duration of episode within the range of 20 days and 386 days, as indicated by the 1<sup>st</sup> and 99<sup>th</sup> percentiles.

Over the 9-year period, mean ( $\pm$ SD) cumulative treatment duration was 142 ( $\pm$ 253) days and 152 ( $\pm$ 251) days per patient, with a median (inter quartile range) of 56 (28, 125) and 58 (28, 151) days for younger and elderly patients, respectively. Therefore, Oxytrol was cumulatively used for an average of about five months ( $\pm$ 8 months) with median of about two months overall. About 21% - 24% of patients have cumulatively used Oxytrol for 91-360 days and about 10% used over 360 days. Again, the distribution was widely spread out; cumulative duration fell between 21 and 1,337 days for 98% of younger patients and between 24 to 1,297 days for elderly patients.

The median of the longest episode observed for each patient during the study period was 30 days; however, 17% - 19% lasted for 91-360 days, and 3.4% - 3.6% lasted over 360 days.

For males, the mean ( $\pm$ SD) number of dispensings per patient during the study period was 5 ( $\pm$ 9) prescriptions for younger patients and 4 ( $\pm$ 7) prescriptions for elderly patients, with a median of 2 prescriptions. The mean ( $\pm$ SD) number of episodes per patient was 2 ( $\pm$ 3) episodes, with a median (inter quartile range) of 1 (1, 2) episode for both male age groups. The mean ( $\pm$ SD) duration of episodes per patient was 62 ( $\pm$ 89) days for younger and 62 ( $\pm$ 77) days for elderly patients, with a median of 30 days.

Similar cumulative treatment duration patterns were seen in males. Over the 9-year period, mean ( $\pm$ SD) cumulative treatment duration was 153 ( $\pm$ 272) days for younger and 135 ( $\pm$ 215) days for elderly male patients with a median of 56 days. About 21%-24% of

patients have cumulatively used Oxytrol for 91-360 days and 9%-11% used Oxytrol over 360 days. The median of the longest episode was 30 days; however, 18%-19% lasted for 91-360 days, and 3%-4 % lasted over 360 days.

#### 4 DISCUSSION

The purpose of this review is to assess patient exposure and treatment duration for Oxytrol users in U.S. outpatient retail pharmacies. Our findings show that approximately 23,000 Oxytrol users nationwide received a dispensed prescription in year 2011 from outpatient retail pharmacies; an 86% decrease in patients since year 2004. On average, there were about 3-4 times more prescriptions dispensed annually than there were patients who received prescriptions, indicating that there were some patients who received more than 1 prescription per year.

Duration of use analysis showed that the majority (82.5% of patients) of Oxytrol users were female. Among female users, the mean ( $\pm$ SD) duration of an episode of use was 60 ( $\pm$ 78) days for patients younger than 65 years old and 63 ( $\pm$ 79) days for patients 65 years and older, with a median duration of 30 days per episode for both age groups. High variability was observed due to extreme values in the data; about 75% of patients had episodes that lasted  $\leq$ 2 months, and only about 1% of patients had episodes that lasted longer than one year.

Over the 9-year study period, mean ( $\pm$ SD) cumulative treatment duration was 142 ( $\pm$ 253) and 152 ( $\pm$ 251) days for patients under 65 years of age and patients 65+ years of age, respectively. The median cumulative treatment duration was 56 days for patients under 65 years of age and 58 days for patients 65+ years of age. Again, we observed high variability in the data. However, about 75% of patients had total treatment not exceeding five months, and only about 1% of patients had extremely long total treatment duration longer than 3.5 years. Duration of use did not differ significantly between patients under 65 years of age and patients 65+ years of age. Further, similar patterns of use were observed between male and female patients.

Our analysis included all Oxytrol users since approval of the drug in 2003. However, by not restricting patients to incident users (new users), we have included patients who might have entered the database with previous prescriptions of Oxytrol under other insurance. Inclusion of such patients can underestimate the duration of use. In addition, we followed all patients until the end of the study period (2011), without censoring episodes that may continue beyond the study period, to capture full duration of episode. This might also underestimate the duration of episode for those having prescriptions close to the end of follow up period.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that Oxytrol was distributed primarily (51%) in outpatient settings based on the IMS Health, IMS National Sales Perspectives<sup>TM</sup>. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. We focused our analysis on only the outpatient retail

pharmacy setting, therefore these estimates may not apply to other settings of care in which these products are used (e.g. mail order).

There are also several limitations in the current duration of use analysis. First, the database used does not cover mail order, while 28% Oxytrol is distributed through mail order. The use of mail order prescriptions may impact the duration of episodes, as well as cumulative treatment duration. We assume very few patients switch back and forth between mail order and retail prescriptions for Oxytrol. However, if a patient did switch from retail prescriptions to mail order, the actual treatment duration will be underestimated in our analysis. Second, duration was determined based on days' supply of prescription dispensing. We do not know if the patients actually used the patches or whether dispensing pharmacists accurately estimated the days supply. In this situation, the actual treatment duration may be longer than our estimates.

## **5 CONCLUSIONS**

Patient exposure to Oxytrol significantly decreased since product approval in year 2003. In year 2011, approximately 92,000 prescriptions for Oxytrol were dispensed and approximately 23,000 patients received a dispensed prescription in the outpatient retail pharmacy setting. Oxytrol utilization in elderly patients aged 65+ years, accounted for the majority of utilization (62% of prescriptions and 59% of patients) during the examined time.

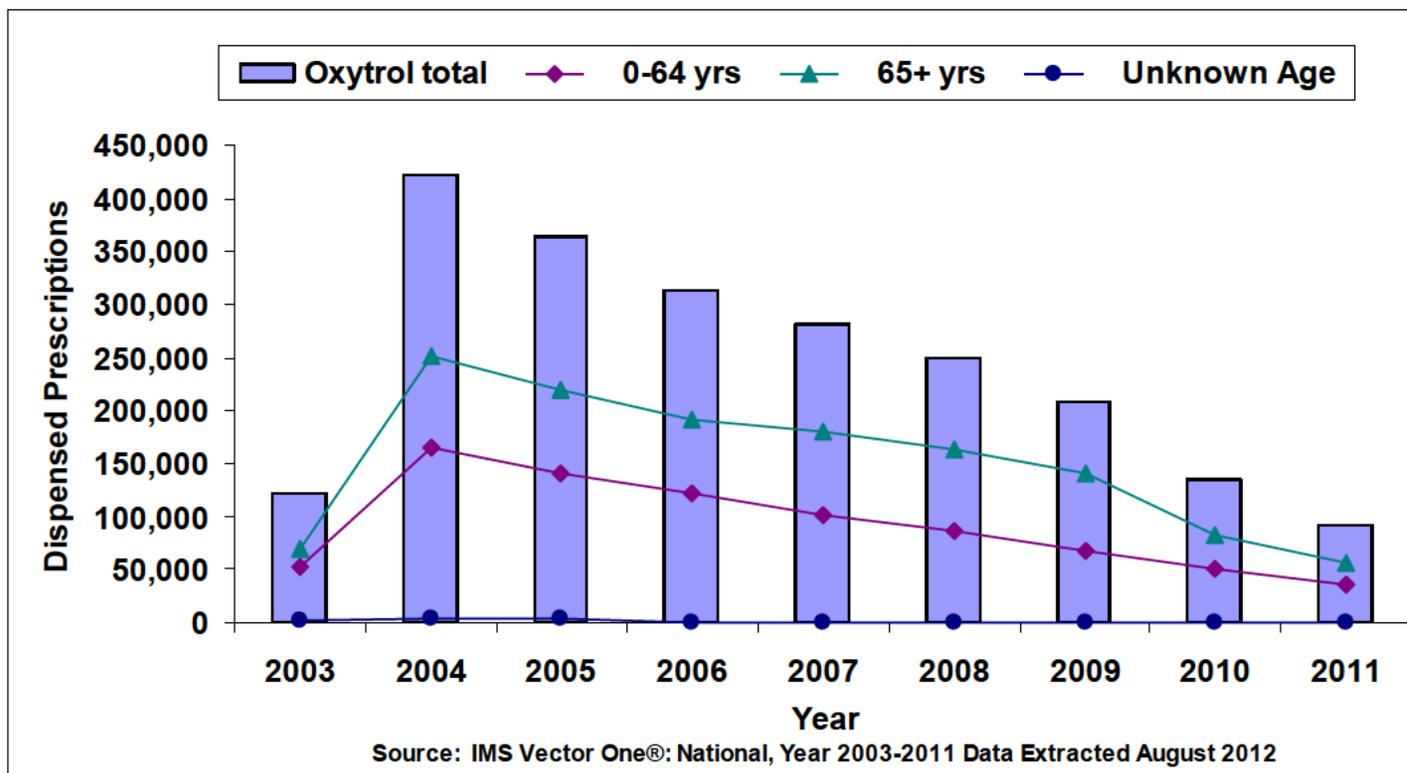
In the study population, the majority (82.5% of patients) of Oxytrol users were female, of which 75% had 1 to 2 treatment episodes during the 9-year study period. The mean and median duration of episodes were about two months and one month, respectively. High variability was observed due to extreme values in the data; however, about 75% of patients had episodes that lasted for  $\leq 2$  months. Additionally, the mean and median cumulative (total) treatment duration during the entire study period was about five months and two months, respectively. Again, the range of total treatment duration varied, but about 75% of patients had total treatment not exceeding five months.

Duration of use did not differ significantly between patients under 65 years of age and patients 65+ years of age.

## 6 APPENDICES

### 6.1 APPENDIX 1: TABLES AND FIGURES

Figure 1. Nationally estimated number of dispensed prescriptions for Oxytrol patch by patient age (0-64, 65+) in U.S. outpatient retail pharmacies, 2003-2011



**Table 1. Nationally estimated number of dispensed prescriptions for Oxytrol patch by patient age (0-64, 65+) in U.S. outpatient retail pharmacies, 2003-2011**

	2003		2004		2005		2006		2007		2008		2009		2010		2011		01/2003-12/2011	
	TRxs	Share	TRxs	Share	TRxs	Share														
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<b>Oxytrol</b>	<b>122,384</b>	<b>100.0%</b>	<b>421,774</b>	<b>100.0%</b>	<b>363,708</b>	<b>100.0%</b>	<b>313,441</b>	<b>100.0%</b>	<b>281,575</b>	<b>100.0%</b>	<b>248,973</b>	<b>100.0%</b>	<b>208,678</b>	<b>100.0%</b>	<b>134,178</b>	<b>100.0%</b>	<b>91,788</b>	<b>100.0%</b>	<b>2,186,499</b>	<b>100.0%</b>
<b>0 - 64 yrs</b>	52,305	42.7%	165,338	39.2%	140,584	38.7%	121,339	38.7%	100,698	35.8%	85,855	34.5%	68,275	32.7%	50,833	37.9%	34,969	38.1%	820,197	37.5%
<b>65+ yrs</b>	69,055	56.4%	251,826	59.7%	219,346	60.3%	192,094	61.3%	180,877	64.2%	163,117	65.5%	140,280	67.2%	83,323	62.1%	56,819	61.9%	1,356,737	62.1%
<b>Unknown Age</b>	1,024	0.8%	4,610	1.1%	3,778	1.0%	8	0.0%	0	0.0%	0	0.0%	123	0.1%	23	0.0%	0	0.0%	9,566	0.4%

Source: IMS Vector One®: National, Years 2003-2011 Data Extracted August 2012. File: VONA 2012-1208 Oxytrol TRx by age 8-27-12

**Table 2. Nationally estimated number of patients (ages 0-64, 65+) who filled a prescription for Oxytrol patch in U.S. outpatient retail pharmacies, 2003-2011**

	2003		2004		2005		2006		2007		2008		2009		2010		2011		1/2003-12/2011	
	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<b>Oxytrol</b>	<b>69,365</b>	<b>100.0%</b>	<b>161,506</b>	<b>100.0%</b>	<b>114,242</b>	<b>100.0%</b>	<b>93,536</b>	<b>100.0%</b>	<b>82,589</b>	<b>100.0%</b>	<b>69,625</b>	<b>100.0%</b>	<b>54,045</b>	<b>100.0%</b>	<b>34,275</b>	<b>100.0%</b>	<b>22,873</b>	<b>100.0%</b>	<b>481,356</b>	<b>100.0%</b>
<b>0 - 64 yrs</b>	32,539	46.9%	72,079	44.6%	49,310	43.2%	36,955	39.5%	29,956	36.3%	24,332	34.9%	17,819	33.0%	12,726	37.1%	8,692	38.0%	200,525	41.7%
<b>65+ yrs</b>	36,889	53.2%	89,821	55.6%	65,308	57.2%	56,936	60.9%	52,974	64.1%	45,624	65.5%	36,467	67.5%	21,757	63.5%	14,343	62.7%	285,155	59.2%
<b>Unknown Age</b>	38	0.1%	34	0.0%	12	0.0%	6	0.0%	0	0.0%	0	0.0%	23	0.0%	13	0.0%	0	0.0%	108	0.0%

Source: IMS Total Patient Tracker. Years 2007-2010 Data Extracted Month-2011 File: File\*.xls

\*Subtotals may not sum exactly, due to rounding. Due to aging of patients during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.

**Table 3.** Patient characteristics of Oxytrol users, IMS Data Extract Tool, 2003-2011

Age at first dispensing (years)	Female		Male	
	(N=190,287)		(N=40,336)	
Mean (SD)	65.1 (16.2)		67.5 (17.9)	
0-64 (n, %)	82,594	43.4%	12,242	30.4%
65+ (n, %)	107,693	56.6%	28,094	69.6%

**Table 4.** Duration of Oxytrol use, by age groups (0-65 and 65+) and gender, IMS Data Extract Tool, 2003-2011

	Female		Male	
	0-64	65+	0-64	65+
<b>Number of patients</b>	82,594	107,693	12,242	28,094
<b>Number of dispensing per patient</b>				
Mean (SD)	4.5 (8)	4.8 (8)	5.1 (9.3)	4.3 (6.8)
Median	2	2	2	2
Interquartile range	1, 4	1, 5	1, 5	1, 4
<b>Number of episodes per patient</b>				
Mean (SD)	2.2 (2.9)	2.3 (2.9)	2.3 (3.1)	2.1 (2.6)
Median	1	1	1	1
Interquartile range	1, 2	1, 2	1, 2	1, 2
Patient with one episode (%)	63.2%	60.3%	62.7%	62.5%
<b>Mean duration of episodes per patient</b>				
Mean (SD)	60.2 (77.8)	63.4 (79)	62.1 (88.5)	61.7 (77.1)
Median	30	30	30	30
Interquartile range	28, 61	28, 70	28, 62	28, 66
1 <sup>st</sup> percentile, 99 <sup>th</sup> percentile	20, 386	20, 384	15, 430	17, 358
<b>Cumulative treatment duration per patient</b>				

Mean (SD)	142.3 (252.9)	152.3 (250.6)	153.1 (271.7)	135.4 (215)
Median	56	58	56	56
Interquartile range	28, 125	28, 151	28, 141	28, 140
1 <sup>st</sup> percentile, 99 <sup>th</sup> percentile	21, 1337	24, 1297	15, 1398	21, 1123
≤30 (%)	43.7%	39.6%	44.2%	41.2%
31-90 (%)	25.5%	25.4%	23.5%	25.5%
91-360 (%)	21.4%	24.3%	21.3%	24.3%
>360 (%)	9.5%	10.7%	11.0%	9.0%
<b>Duration of longest episode</b>				
Mean (SD)	81.7 (123.7)	87 (126.1)	87 (137.9)	81.3 (114.7)
Median	30	30	30	30
Interquartile range	28, 84	28, 88	28, 85	28, 85
≤30 (%)	54.9%	50.5%	54.5%	51.8%
31-90 (%)	25.0%	26.5%	23.4%	26.6%
91-360 (%)	16.7%	19.4%	18.0%	18.8%
>360 (%)	3.4%	3.6%	4.0%	2.8%

---

## 6.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

### **IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### **IMS, Vector One®: National (VONA)**

The IMS, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

### **IMS, Vector One®: Total Patient Tracker (TPT)**

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

### **IMS, Vector One®: Data Extract Tool**

The IMS, Vector One®: Data Extract Tool (DET) is a population based dataset containing prescriptions dispensed from approximately 54,000 U.S. retail pharmacies, accounting for approximately 50% of the prescriptions dispensed in the U.S. Prescription records are linked to a unique patient identifier, allowing each prescription to be associated with a unique patient as they receive prescriptions from different pharmacies. The following data elements are available for each prescription record: patient age, gender, unique patient ID, product name, product strength, product form, prescription date, new Rx/refill Rx indicator (Fill Sequence #), days supply, prescriber specialty, quantity dispensed, method of payment (third party, cash, Medicaid, Medicare), unique pharmacy ID, pharmacy state, pharmacy zip, pharmacy city, unique prescriber ID, unique payor ID, prescription reference number.

Data used in DET is derived from IMS' Vector One® database. The Vector One® database integrates prescription activity from a variety of sources, including national retail chains, mass merchandisers, food stores and their data systems, and provider groups. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients. DET is a prescription claims-level database designed to give users a detailed view of claims entering the Vector One® data warehouse.

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

/s/  
-----

PATTY A GREENE

10/10/2012

drug use data cleared by data vendor 10/8/12

GRACE CHAI

10/11/2012

ESTHER H ZHOU

10/11/2012

TAREK A HAMMAD

10/11/2012

JUDY A STAFFA

10/15/2012

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information	
NDA # 202211 BLA#	NDA Supplement #:S- BLA Supplement #
Efficacy Supplement Type SE-	
Proprietary Name: Oxytrol for Women Established/Proper Name: oxybutynin Dosage Form: patch Strengths: 3.9mg	
Applicant: MSD Consumer Care, Inc. Agent for Applicant (if applicable):	
Date of Application: 3/26/2012 Date of Receipt: 3/26/2012 Date clock started after UN:	
PDUFA Goal Date: 1/26/2013	Action Goal Date (if different): 1/25/2013
Filing Date: 5/25/2012	Date of Filing Meeting: 4/24/2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) 8a	
Proposed indication(s)/Proposed change(s): over-the-counter relief of symptoms of over-active bladder in adult women	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>	
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input checked="" type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ): Division of Reproductive and Urologic Products				
List referenced IND Number(s): 074288				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  <i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1444 1349 1583"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>x</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>	Electronic review aid			
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?<sup>1</sup>            If not, explain (e.g., waiver granted).</p>	X			mixed
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>			X	

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>			X	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>			X	
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>			X	
<b>Prescription Labeling</b>	<input checked="" type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>				

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?				
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?				
<b>OTC Labeling</b>	<input type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Outer carton label <input checked="" type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input checked="" type="checkbox"/> Other (specify) 14 ct Backer Card			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	X			
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> 10/13/2009  <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 9/12/2011  <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 4/24/12

**BLA/NDA/Supp #:** 202211

**PROPRIETARY NAME:** Oxytrol for Women

**ESTABLISHED/PROPER NAME:** oxybutynin

**DOSAGE FORM/STRENGTH:** patch 3.9 mg/day

**APPLICANT:** MSD Consumer Care Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** over-the-counter relief of symptoms of over-ctive bladder in adult women

**BACKGROUND:** MSD Consumer Care, Inc submitted an original NDA under 505(b) of the FDCA to change the marketing status of Oxytrol (oxybutynin) transdermal system, NDA 21-351, from Rx to over-the-counter. This is a partial Rx to OTC switch as the OTC product is proposed for women ages 18 and older for the relief of overactive bladder symptoms. The Rx is indicated for men and women. Watson Pharmaceuticals, Inc., the holder of NDA 21-351 for the Rx Oxytrol transdermal system, has granted MCC the right of reference to the data in their NDA.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Phong Do	y
	CPMS/TL:	Melissa Furness	y
Cross-Discipline Team Leader (CDTL)	Lesley-Anne Furlong		y
Clinical DNCE	Reviewer:	Ryan Raffaelli	y
	TL:	Lesley-Anne Furlong	y
Clinical DRUP	Reviewer:	Donald McNellis	y
	TL:	Suresh Kaul	y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	Barbara Cohen	y
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	Maria Ysern	y

	TL:	Betsy Scroggs	y
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:		
	TL:		
Biostatistics	Reviewer:	Yunfan Deng	y
	TL:	Yan Wang	y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Cindy Li	y
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Shelly Markofsky	y
	TL:	Swapan De	y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	James Schlick	y
	TL:	Todd Bridges	n
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Sharon Gershon/Susan Thompson OSI		
Other attendees	Andrea Leonard Segal, Director, DNCE Joel Schiffenbauer, D. Director, DNCE Charles Ganley, Director, ODEIV Audrey Gassman, Acting D. Director, DRUP Julie Beitz, Director ODEIII Victoria Kusiak, D. Director ODEIII		y

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<p><b>Comments:</b> See Clinical Filing review</p>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date if known: TBD <input type="checkbox"/> NO

<p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> Info requests: see Biostats filing review</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b> Info Requests: see nonclinical filing review	<input checked="" type="checkbox"/> Review issues for 74-day letter
---	---

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b> ONDQA- TBD if micro needed.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Office Level - Charles Ganley, Director ODE IV & Julie Beitz, Director ODEIII	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): Will send out prior to 74 day letter via an information request.  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

	filing letter; For NDAs/NDA supplements: see CST for choices)
	<ul style="list-style-type: none"> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

Phong Do	4/26/12
Regulatory Project Manager	Date
Melissa Furness	5/7/12
Chief, Project Management Staff	Date

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/  
-----

PHONG DO  
05/31/2012

# Filing Checklist for Oxytrol for Women (oxybutynin) Transdermal System

---

---

**SUBMISSION DATES:** March 26, 2012

**NDA/SUBMISSION TYPE:** NDA 202-211

**ACTIVE INGREDIENTS:** Oxybutynin 3.9 mg/day

**DOSAGE FORM** Transdermal System

**SPONSOR:** MSD Consumer Care, Inc.  
556 Morris Avenue  
Summit , NJ 07901  
Authorized US Agent:  
Nancy Pierro, Associate Director, Regulatory Affairs  
908-473-5709  
Fax : (908) 473-3814

**REVIEWER:** Maria Ysern, IDS, DNRD, ODE IV

**TEAM LEADER:** Betsy Scroggs, PharmD, DNRD, ODE IV

**REGULATORY PROJECT  
MANAGER** Do Phong, PharmD, Lieutenant-USPH, DNCE, ODE IV

---

---

<b>Submitted Labeling</b>	<b>Representative of Following SKUs</b>
1-Count Immediate Container (Pouch)	The same one-count pouch will be used for each package size.
4-Count Carton	2- Count and 8-Count Carton. All identical to the 4-count with the exception of count – size specific information)
10-Count Carton	10-Count Bonus Pack Carton
14-Count Club Store Pack Backer Card (This component is a card, printed on both sides. The front has a window for display of the 14-count carton's PDP. The printed back of the card, will contain the Drug Facts).	13- and 15-Count Club Store Pack
14-Count Club Store Pack Backer Card (Submitted example shows how the 14-count carton's principal display panel appears through the card's front window)	13- and 15-Count Club Store Pack

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	No	It is a New NDA
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	No	4 count carton, 10 count carton, 14 count package and one count pouch are representative of the following planned commercial sizes: 2-, 4-, and 8-count cartons 10-count bonus pack carton 13-, 14-, and 15- count club store pack. <i>The sponsor has submitted the Rx Consumer Information Leaflet. They need to submit one for the OTC product.</i>
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	YES	-
Is distributor labeling included?	No	-
Does the submission include the annotated specifications for the Drug Facts label?	YES	
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	Yes	-
Do any of the labels include "prescription strength" or similar statements?	YES	"Full Prescription Strength" The review team is aware of this proposed statement.
Do any of the labels include "#1 doctor recommended" or similar endorsement statements?	No	
Do any labels include text in a language other than English?	No	
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	Yes	DMEPA is reviewing the proposed trade name.
Does a medical officer need to review any clinical issues?	Yes	An MO is assigned to review this NDA
If SLR, should ONDQA also review?	NA	Not SLR, this is NDA and ONDQA is assigned

**REVIEWER COMMENTS:**

The sponsor has not submitted an OTC Consumer Information Leaflet.

The appropriateness of the proposed statement “Full Prescription Strength” is being evaluated by the team. The review team is aware.

All the labels need to be submitted to be reviewed not only the representative ones.

**Information Request:**

- a. Please submit an OTC Consumer Leaflet Information.
- b. Submit all of the proposed labels for review, not only representative labeling.
- c. Please clarify if the 2-count package is retail or a sample-size.

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

/s/  
-----

MARIA E YSERN  
05/07/2012

RUTH E SCROGGS  
05/07/2012

## DSI CONSULT: Request for Clinical Inspections

**Date:** 4/20/12

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2  
*Sharon Gershon, Pharm.D., Primary Reviewer*  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** *Ryan Raffaelli, M.D., Medical Officer,, DNCE*  
*Lesley Anne Furlong, M.D., Team Lead, DNCE*

**From:** *Phong Do, Regulatory Health Project Manager, DNCE*

**Subject:** **Request for Clinical Site Inspections**

### **I. General Information**

Application#: NDA-202211  
Applicant/ Applicant contact information (to include phone/email):  
MSD Consumer Care, Inc.  
556 Morris Ave  
Summit, NJ 07901  
Nancy Pierro, Associate Director Regulatory Affairs  
[Nancy.pierro@merck.com](mailto:Nancy.pierro@merck.com)  
(908) 473-5709  
(908) 473-3814 (Fax)  
Drug Proprietary Name: Oxytrol for Women  
NME or Original BLA (Yes/No): No  
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No  
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Relief of overactive bladder symptoms

PDUFA: 1/26/13

Action Goal Date: 1/25/13

Inspection Summary Goal Date: There will be an advisory committee meeting for the application, but the timing has yet to be determined. We tentatively request that inspections be completed by the end of September 2012. We will be able to update the timeline after the AC planning meeting scheduled in mid-May.

DSI Consult  
version: 5/08/2008

**II. Protocol/Site Identification**

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #10 (rank #1) Stevenson Family Pharmacy 6201 King Hill Ave. St. Joseph, MO 64504 Deanne Jungbluth (b) (6) P: 816-238-2424 F: 816-238-6717	CL2008-13	56 subjects	Relief of overactive bladder symptoms
Site #12 (rank #3) Matt’s Medicine Store 11200 1/2 E.US Highway 24 Independence, MO 64054 Charles Mallinson (b) (6) P: 816-833-3636 F: 816-833-1071	CL2008-13	52 subjects	Relief of overactive bladder symptoms
Site #24 (rank #13) Catonsville Pharmacy 6350 Frederick Rd. Baltimore, MD 21228 Neil Leikach (b) (6) P: 410-744-5959 F: 410-744-4810	CL2008-13	26 subjects	Relief of overactive bladder symptoms
(b) (4)			

**III. Site Selection/Rationale**

Sites #10 and 12 were the highest enrollers and had the highest number of discontinuations. Site #12 reported the highest number of serious AEs (7). Site #24 had the highest number of discontinuations as a percentage of those enrolled at the site (27%). The site also reported two serious AEs, including one death. These three sites also had several protocol deviations where

subjects were not consented with up-to-date versions of the Informed Consent Form. (b) (4) is the CRO and keeps the trial master file and source data.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):
  - High percentage of discontinuations and protocol deviations
  - Death reported
  - CRO site

Should you require any additional information, please contact Phong Do at 301-796-4795 or Ryan Raffaelli at 301-796-2376.

Concurrence:

- Lesley Furlong, MD Medical Team Leader
- Ryan Raffaelli, MD. Medical Reviewer

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

/s/  
-----

PHONG DO  
04/20/2012