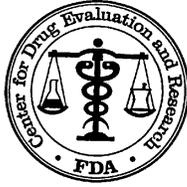


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202211s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 202211
Supplement #: 0000
Drug Name: OXYTROL for Women
Oxybutynin Transdermal System, 3.9 mg/day
Indication(s): Relief of overactive bladder symptoms
Applicant: Merck Consumer Care, Inc. (MCC)
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1 EXECUTIVE SUMMARY

Conclusions and Recommendations

In this submission, the Applicant seeks approval of changing the marketing status of Oxytrol (oxybutynin) transdermal system from prescription (Rx) to over-the-counter (OTC). The OTC product is proposed for women ages 18 and older for the relief of overactive bladder symptoms.

The process that led to the currently proposed label for OXYTROL as an OTC product was iterative, and was based on FDA feedback and consumer label study results. Consumer label comprehension and self-selection studies were conducted throughout the label development process.

The Applicant also conducted an actual use study (AKA CL2008-13) to evaluate post-selection behavior and actual use among subjects who purchased the OXYTROL® Transdermal System, in a large sample to represent the projected population of potential OTC purchasers of the drug.

This statistical review will be mainly focused on the actual use study (AKA CL2008-13) and the pivotal label comprehension study (protocol #10053).

For the pivotal label comprehension study (protocol #10053), for the general population cohort:

Of the six communication objectives with higher medical consequence, two endpoints exceeded the pre-defined 90% threshold for success -- the lower bound of the 95% confidence interval (CI) was above 90%: allergic to oxybutynin (95.1%, [95% CI: 92.8%, 96.9%]) and allergic reaction to the patch (93.2% [95% CI: 90.6%, 95.3%]). Three endpoints were within 5 points of the threshold: urinary retention (91.3% [95% CI: 88.4%, 93.7%]), gastric retention (89.9% [95% CI: 86.7%, 92.4%]) and developed blisters and red, itchy skin (88.6% [95% CI: 85.3%, 91.3%]). The endpoint related to narrow angle glaucoma missed the threshold by 5.6 points (87.7% [95% CI: 84.4%, 90.5%]).

Of the communication objectives with lower medical consequences, one endpoint exceeded the pre-defined 85% threshold: kidney stones (89.8% [95% CI: 86.7%, 92.4%]). Three endpoints were within 5 points of the threshold: have OAB symptoms for at least 3 months (87.3% [95% CI: 83.9%, 90.2%]), using a diuretic (87.1% [95% CI: 83.7%, 90.0%]) and liver disease (83.9% [95% CI: 80.3%, 87.1%]). Finally, for stress incontinence, the point estimate was 77.3% with 95% CI of [73.3%, 81.0%].

For the women aged 44+ with diabetes risk factors cohort: Both of the primary objectives related to the diabetes warnings were within three points of meeting the 85% threshold (History of diabetes: 88.8% [95% CI: 82.8%, 93.2%]; Diabetes symptoms: 88.1% [95% CI: 82.1%, 92.7%]).

For the actual use study CL2008-13, post mitigation, the proportion of subjects who did not stop use when they either developed a new symptom referred to anywhere in the label or when their condition worsened including abdominal and/or pelvic pain was 3.4% (25/727) with 95% CI of

(2.2%, 5.0%). The upper bound of the confidence interval meets the pre-defined target threshold of 5%.

In the actual use study CL2008-13, of the 1069 subjects who made an Oxytrol purchase decision, 839 subjects (78.5%) made a positive purchase decision and had ineligibilities according to the label.

The statistical reviewer does not identify any statistical issues that may preclude the approval of this NDA. However, as the clinical implication of such high label ineligibility rate (78.5%) is beyond the scope of statistical evaluation, the statistical reviewer defers the decision of approval of this NDA to the clinical review team.

Brief Overview of Clinical Studies

Pivotal Label Comprehension Study (Protocol #10053) Conducted in Late 2010

This was a multi-site, single visit label comprehension study among a population of female respondents who self-reported OAB symptoms or diabetes risk factors. This multi-site study was conducted in nine (9) geographically dispersed market research facilities. Potential respondents were screened over the phone using the inclusion/exclusion criteria on the screener. Qualified respondents were directed to the market research site. The study was completed with 752 respondents. Cohort 1 (General Population) included 472 subjects. Almost 7% (n=32) of the general population tested as low literate. Cohort 2 (Enriched Low Literacy Sample) included 120 subjects. Cohort 3 (Women 44+ with Diabetes Risk Factors) included 160 respondents.

Actual Use Study (AKA CL2008-13)

The Applicant also conducted an actual use study CL2008-13, also known as CONTROL (CONsumer TRial of OXYTROL) study. The study was a comprehensive, large-scale, naturalistic actual use study. CONTROL was designed to evaluate post-selection behavior and actual use among subjects who purchased the OXYTROL® Transdermal System, in a large sample to represent the projected population of potential OTC purchasers of the drug. In order to allow a more naturalistic population to participate, the CONTROL study was not designed to rigorously assess self-selection.

CONTROL was an open-label, 15-week study conducted in 10 metropolitan areas in the United States at 26 retail pharmacies. This 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. Telephone-based follow-up interviews and subject use diaries were used to collect product usage data.

There were 2,731 subjects who responded to the recruitment advertisement and underwent the initial screening; of these subjects, 1230 entered the enrollment phase, evaluated/read the Oxytrol package and the Drug Facts label, made a purchase decision, took the REALM test, and underwent an eligibility screening interview. Eighty percent (856 subjects) of the 1070 subjects

who wanted to purchase Oxytrol for their own use were allowed to enter the 12-week actual use phase. There were 727 verified users in the study.

The following is the listing of other consumer behavior studies conducted during the OTC label development process and the detailed discussion of these studies is provided in Sections 4 and 5.

Label Comprehension Studies:

- Full Label Comprehension Study Among 65+ Women (Protocol #92101) Conducted in Early 2010
- Targeted Label Comprehension Study of Diabetes Warnings (Protocol #92099) Conducted in Early 2010
- Targeted Label Comprehension Study of Enhanced Pregnancy Warning (Protocol #92062) Conducted in Early 2010
- Initial 2008 Label Comprehension Study (Protocol #82023) Conducted in 2008

Self-Selection Studies:

- Targeted Self-Selection Study in Pregnant Women (Protocol #10054) Conducted in late 2010
- Targeted Self-Selection Study in Men (Protocol #92061) Conducted in late 2009
- Initial Self-Selection Study (Protocol #CL2008-19) Conducted in early 2009

2 INTRODUCTION

2.1 Overview

This submission proposes the prescription to over-the-counter switch of OXYTROL® for Women (Oxybutynin Transdermal System {TDS} 3.9mg/day) to treat overactive bladder (OAB). OAB is defined as urgency, with or without urge incontinence, usually with frequency and nocturia. It is commonly described as the overactive bladder syndrome, urge syndrome or urgency-frequency syndrome. These symptom combinations are suggestive of urodynamically demonstrable detrusor overactivity, but can be due to other forms of urethro-vesical dysfunction. These terms can be used if there is no proven infection or other obvious pathology.

OXYTROL is an anticholinergic drug which is indicated for the treatment of OAB. Treatments for OAB include anticholinergics, which act as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle cells. In patients with overactive bladder characterized by detrusor muscle instability or hyperreflexia, cystometric studies have demonstrated that oxybutynin increases maximum urinary bladder capacity and increases the volume to first detrusor contraction.

The OXYTROL patch is designed to deliver oxybutynin continuously and consistently over a (b) (4) 4-day time interval after application to intact skin. Over the past 30 years, transdermal drug delivery has become a proven technology that offers a variety of clinical benefits over other dosage forms. By delivering drug directly into systemic circulation via skin application and bypassing first-pass gastric and hepatic metabolism, transdermal agents are able to improve

tolerability, promote better adherence and avoid peaks and troughs seen with oral agents as they reach therapeutic concentration. Oxybutynin TDS has a skin contact surface area of 39 cm² and contains 36 mg of oxybutynin. Oxybutynin TDS provides efficacy comparable to other FDA approved oxybutynin therapies and provides a statistically significant reduction of OAB symptoms compared to placebo.

2.2 Data Sources

The Applicant's study datasets for the actual use study and all the label comprehension and self-selection studies are available at <\\cdsesub4\NONECTD\NDA202211\5042716>

At the pre-NDA meeting, we requested the data format for the actual use study (CONTROL) including the following flag variables for each type of conditions stated in the label:

- Condition worsens
- New symptoms appear
- Condition does not improve after 2 weeks of use
- Having an allergic reaction to the product
- Having severe redness, itchiness, or blistering at the site of application

However, those variables were not submitted in the initial NDA submission for the primary endpoint dataset. Although the applicant's analysis results for the primary and key secondary endpoints can be reproduced following the instructions provided in the submission, it was very difficult to understand how the results were derived from the program codes. Therefore, the statistical reviewer requested the following information to be provided by the Applicant during the review:

Please resubmit the primary endpoint dataset with the following 24 flag variables (12 for pre-mitigation and 12 for post-mitigation) included:

- *One flag for "condition worsens" and one flag indicating whether the user stop use or not when his/her condition worsens*
- *One flag for "new symptoms appear" and one flag indicating whether the user stop use or not when his/her new symptoms appear*
- *One flag for "condition does not improve after 2 weeks of use" and one flag indicating whether the user stop use or not when his/her condition worsens*
- *One flag for "having an allergic reaction to the product" and one flag indicating whether the user stop use or not when his/her having an allergic reaction to the product*
- *One flag for "having severe redness, itchiness, or blistering at the site of application" and one flag indicating whether the user stop use or not when his/her having severe redness, itchiness, or blistering at the site of application*
- *One flag for "having abdominal and/or pelvic pain" and one flag indicating whether the user stop use or not when his/her having abdominal and/or pelvic pain*

Please use the following format: 1 for Yes, 2 for No, and 99 for Missing for these variables. Please also submit the program codes used to derive these variables. We expect that these program codes will help us understand how the primary and key secondary endpoints are

derived, and the derived variables will enable us reproduce your results presented in Table 13, 14, 16, 18, and 20 of the study report and perform supportive analyses if needed during our review.

Per the statistical reviewer's request, the Applicant resubmitted the dataset with the above flag variables included and navigating the dataset was much easier afterwards.

All the datasets (raw and derived) were submitted with detailed definition of each variable. Results of the primary and key secondary endpoints can be reproduced by the statistical reviewer. The analysis performed by the Applicant followed the statistical analysis plan (SAP).

3 STATISTICAL EVALUATION

3.1 Actual Use Study

3.1.1 Study Design

Study CL2008-13, also known as CONTROL (CONsumer TRial of Oxytrol) study was an open-label, single-arm, multicenter, actual use study. This study was not intended or designed to rigorously collect self-selection information. In this naturalistic study, some subjects did not strictly meet all of the eligibility criteria in the Drug Facts label were allowed to purchase Oxytrol. This enabled observation of use patterns and safety in subjects who might potentially use the product despite comparing their purchase decision against every label criterion as it was asked during the eligibility assessment.

The study consisted of 4 phases:

(1) An initial recruitment screening

A sufficient number of demographically diverse women were targeted for enrollment ($N \geq 1000$) to obtain at least 531 verified users. Recruitment advertising was developed to attract women who were concerned about their overactive bladder (OAB) condition. Subjects who met the initial screening criteria were directed to 1 of the 26 pharmacy sites where they examined the Oxytrol package and made a purchase decision, "Are you interested in buying this product for your own use or not?" Subjects were not asked to perform a self-selection step. The pharmacist did not volunteer any guidance to interfere with their purchase decision; however, if the subject asked about Oxytrol, the pharmacist addressed and recorded the questions.

(2) An onsite enrollment eligibility interview

Regardless of their purchase decision, subjects underwent an enrollment interview where their eligibility for using Oxytrol was assessed. The pharmacist inquired and recorded subjects' OAB condition, medical history, and demographics. Subjects then took The Rapid Estimate of Adult Literacy in Medicine (REALM1) test. Subjects, who reported having narrow-angle glaucoma,

were breastfeeding, or who were allergic to oxybutynin were not allowed to enter the use phase. Their reasons for wanting to purchase Oxytrol were recorded and they were compensated for their time until that point. Subjects who reported having symptoms of blood in the urine not related to menses, back pain and fever in conjunction with frequency or urgency, dysuria, hematuria, or cloudy urine were also excluded from the use phase and advised to see a physician for medical evaluation. They were asked to provide informed consent, allowing the study nurse to conduct a follow-up telephone interview with them and, with an additional consent, to contact their doctor for the diagnosis outcomes and the medical records. Subjects who did not meet any of the above-mentioned exclusion criteria were invited to enter the 12-week actual use phase.

(3) A 12-week actual use phase

They signed the informed consent form, provided contact information, completed the purchase process, and women of childbearing potential underwent a pregnancy test. They received an Oxytrol package with a Drug Facts label similar to the final proposed label for the actual OTC product. Subjects used Oxytrol based on how they understood the Drug Facts label. They recorded this use on the provided medication diary and participated in 3 follow-up telephone interviews at 3, 7, and 12 weeks after the initial purchase. Subjects returned their patch use diary after each telephone interview. During the use phase, subjects could purchase additional Oxytrol, up to 24 boxes (4 patches per box).

(4) And an end-of-study follow-up interview at Week 15.

Subjects returned to the pharmacy at Week 12 for a urinalysis and participated in the end-of-study interview at Week 15. Subjects who might have misused Oxytrol were questioned regarding reasons for possible misuse. Standardized scripts were used in all the interviews. Throughout the trial, all reported adverse events (AEs) were documented.

3.1.2 Statistical Methodologies

The objective of the study was to evaluate actual use and outcomes of use among subjects who purchased the Oxytrol Transdermal System patch. Accordingly, the following primary and secondary endpoints were assessed.

Efficacy Endpoints

The primary outcome measure for this study was the proportion of subjects who did not stop use when they either developed a new symptom referred to anywhere in the labeling, with the addition of abdominal and/or pelvic pain, or when their condition worsened. This was calculated by dividing the number of subjects in these categories by the total number of subjects who verifiably used the Oxytrol patch at least once. An error rate of 5% or less was the a priori standard set for a successful outcome.

Secondary endpoints were evaluated as follows (no a priori target or performance standard was specified for secondary endpoints):

- Secondary Endpoint 1: The proportion of subjects who did not stop use when they either developed a new symptom referred to anywhere in the Drug Facts labeling (not including abdominal and/or pelvic pain), or when their condition worsened. This was calculated by dividing the number of subjects in these categories by the total number of subjects who verifiably used the Oxytrol patch at least once.
- Secondary Endpoint 2: The median time taken to discontinue Oxytrol use by subjects who did not experience improvement in their symptoms after two weeks of treatment. These data were compiled from follow-up interviews and medication use diaries and a median (number of days) was determined.
- Secondary Endpoint 3: The proportion of subjects who did not stop Oxytrol use within two weeks after experiencing no improvement in their symptoms. This was calculated by dividing the total number of subjects by the number of subjects who used the Oxytrol patch for two weeks.
- Secondary Endpoint 4: For subjects who experienced new symptoms of interest (categorized as shown in the following table) or whose OAB symptoms worsened or who did not improve during Oxytrol treatment and continued on therapy. The proportion of case outcomes with a medical risk, possible medical risk, or minimal/insignificant risk was calculated and evaluated medically. This was calculated as the number of symptoms in each category divided by the total number of case outcomes in all 3 categories.

Risk Level	Risk Level
Medical risk	Narrow-angle glaucoma Were pregnant or breast-feeding Allergic reaction to the product or any of its ingredients Flank or back pain with fever Pain or burning when urinating (with or without fever or chills) but without flank or back pain Blood in the urine Urine that is cloudy or foul-smelling
Possible medical risk	OAB symptoms worsened significantly with abnormal urinalysis Unable to empty bladder completely (urinary retention) Lower back or side pain without fever Diagnosed with gastric retention (or stomach that empties slowly) Diagnosed with liver or kidney disease Unexplained weight loss Begins using a diuretic

Minimal/insignificant medical risk	Condition did not improve OAB symptoms worsened significantly with normal urinalysis
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- Secondary Endpoint 5: Proportion of subjects who incorrectly used the patch (incorrect duration of use and/or simultaneous use). This was calculated by dividing the number of subjects who misused the study medication by the total number of subjects who verifiably used the study drug once (user population). To help provide a comprehensive picture of Oxytrol patch use, Secondary Endpoint 5 was assessed both on the patch level (where the denominator is the total number of patches used across all subjects) and on the subject level.

In addition the following endpoints were analyzed:

- Proportion of subjects who reported an AE and/or an SAE; the characterization and categorization of all AEs and SAEs.
- Combined Primary Endpoint and Secondary Endpoint 3: At the request of the FDA, the proportion of subjects who did not stop use when they either developed a new symptom or when their condition did not improve (worsened or stayed the same) – with the addition of pelvic and abdominal pain.

Populations for Analysis

Screening Population: All subjects who begin the Screening Phase interview.

Enrollment Population: All subjects who complete the Enrollment Phase interview.

Excluded Consent Population: All subjects in the Enrollment Population who were excluded for reporting symptoms of blood in the urine not related to menstrual period and/or back pain and fever in conjunction with frequency or urgency and any of the following: dysuria, hematuria, or cloudy urine, and signed the Excluded Subject Informed Consent. These subjects are excluded from purchasing study drug. If reported, adverse events for these subjects will be collected and the relationship to the study drug will be marked as "unlikely."

Purchaser Population: All subjects who purchased the study medication.

User Population: All subjects from the Purchaser Population who complete at least one follow-up interview. All scenarios of use and non-use are defined within this population

Safety Population: All subjects from the User Population and any subjects in the Excluded Consent Population. Safety Analyses, however, will be conducted separately for the Excluded Consent Population since individuals in this group never actually receive the study medication but are followed up.

Analysis of Primary Outcome

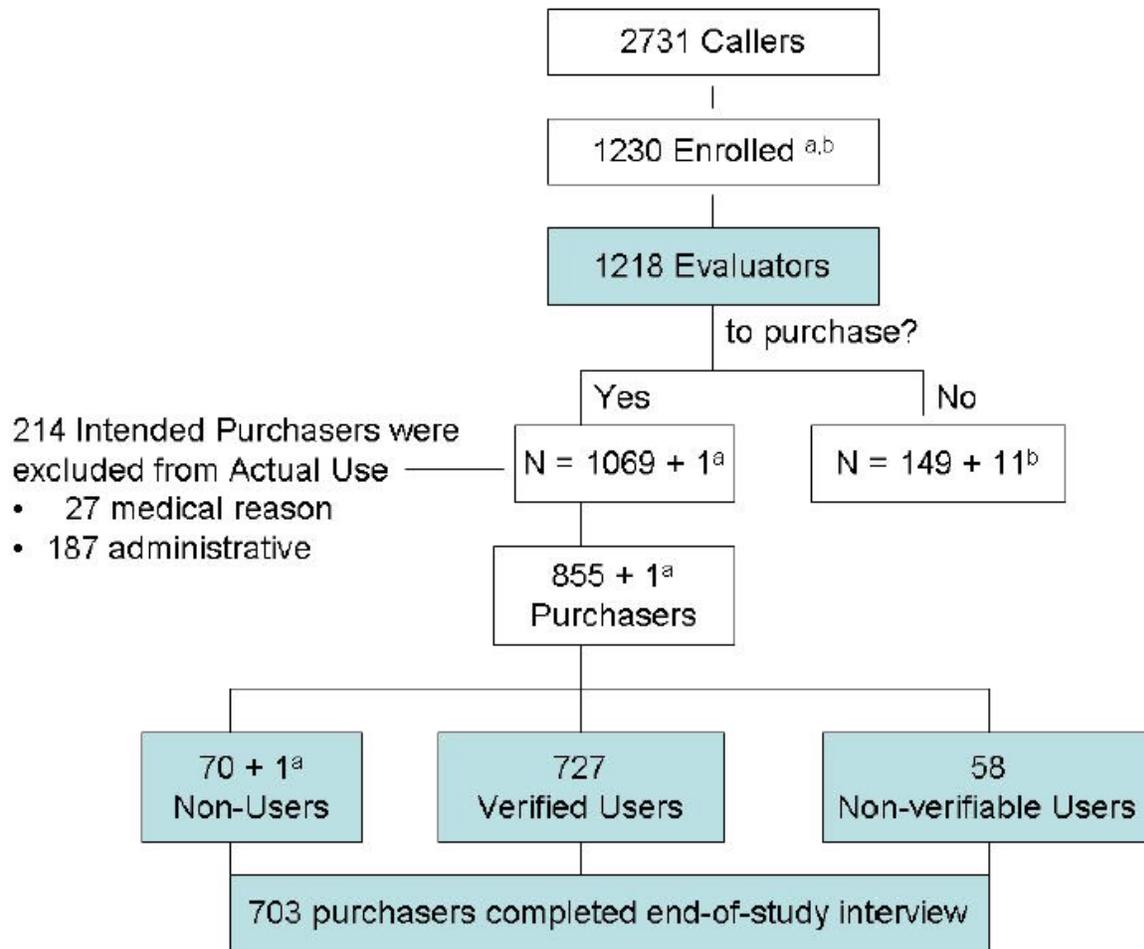
The primary outcome measure for this study was the proportion of subjects who did not stop use when they either developed a new symptom referred to anywhere in the labeling or when their condition worsened. This proportion was presented for both the full User Population and the subset of the User Population who used the product and either developed a new symptom referred to anywhere in the labeling or their condition worsened. This proportion was accompanied by a 95% Exact Confidence interval.

Determination of Sample Size

For those results where the proportion is 50%, a sample of size 1,000 subjects yields a margin of error (i.e. half-width of the confidence interval) of about $\pm 3.1\%$ with 95% confidence. However, those precision levels improve substantially at higher response rates.

3.1.3 Patient Disposition, Demographics, Baseline Characteristics, and Label Ineligibilities

Subject disposition is presented in the following flow chart.



Twelve subjects were excluded from the data analyses.

^a One protocol violator.

^b Eleven subjects with incomplete eligibility data.

Source: Figure 3 of CL2008-13 study report.

There were 2731 subjects who responded to the recruitment advertisement and underwent an initial screening. One thousand two hundred thirty (1230) subjects entered the enrollment phase, evaluated the Oxytrol package and read the Drug Facts label, made a purchase decision, took the REALM test, and underwent an eligibility screening interview.

Eighty percent (N=856) of the 1070 subjects who wanted to purchase Oxytrol for their own use were allowed to enter the 12-week actual use phase. Of the remaining 20% (N=214) who were not dispensed study drug, most (87.4%: 187 of the 214 subjects) were excluded for administrative reasons (e.g., refusal of a pregnancy test), while the remaining 12.6% (N=27) were excluded because of their medical condition.

Eighty-five percent (N=727) of the purchasers had both follow-up and diary data to support their Oxytrol use. Seven percent (N=58) of the purchasers reported their use at the follow-up

interview but didn't have diary data to support their use and 8% of the purchasers (N=71) had neither.

Twelve subjects were excluded from the data analyses, including:

- A protocol violator (Subject 10-0033, a purchaser-nonuser;).
- Eleven subjects who did not complete the eligibility screening interview. These were subjects who decided not to purchase Oxytrol.

In brief, of the 1218 evaluators (subjects who evaluated Oxytrol, read the Drug Facts label, and based on their understanding of the study drug and their own medical condition, made the purchase and use decisions), 70.2% (N=855) purchased Oxytrol and entered the actual use phase and 91.8% (N=785) of the purchasers used Oxytrol at least once. Of the 785 users, 92.6% (N=727) were verified users and 55.4% (N=435) of all users (727 verified and 58 non-verifiable) returned to the pharmacy sites for urinalysis at Week 12.

As shown in the following table, subjects in the CONTROL study were demographically diverse. They included White (72.7%), Black (11.5%), Hispanic (10.8%), and Asian (1.5%) subjects. Subjects' ages were widely distributed and ranged from 18 to 94 years. Subjects aged 40 or younger accounted for 13.4% and subjects age 65 and older accounted for 33.8% of subjects.

Most of the subjects (92.5%) had at least a high school education, and 65.4% had at least some college. The differences among the subgroups (the evaluators, the non-purchasers, the verified-users, and the disqualified intended purchasers) were unremarkable. Out of the 1204 prospective subjects who completed the REALM test, 162 subjects (13.3%) scored less than 61 (i.e., \leq 8th grade level) which was regarded as low literacy for adults.

Table 1: Study CL2008-13 Subjects Demographic Data

	Evaluators (N=1218)	Verified Uses (N=727)	Rejected from Purchasing (N=214)	Non- Purchasers (N=149)
Race and ethnicity				
White	886 (72.7%)	561 (77.2%)	131 (61.2%)	104 (69.8%)
Black or African American	140 (11.5%)	66 (9.1%)	34 (15.9%)	19 (12.8%)
Hispanic or Latino	132 (10.8%)	64 (8.8%)	41 (19.2%)	15 (10.1%)
Asian	18 (1.5%)	12 (1.7%)	1 (0.5%)	4 (2.7%)
Other	42 (3.4%)	24 (3.3%)	7 (3.3%)	7 (4.7%)
Education				
8 th grade or less	17 (1.4%)	9 (1.2%)	4 (1.9%)	3 (2.0%)
Some high school	74 (6.1%)	35 (4.8%)	15 (7.0%)	14 (9.4%)
High school graduate, GED, or certificate	330 (27.1%)	178 (24.5%)	70 (32.7%)	41 (27.5%)
Some college or technical school	454 (37.3%)	283 (38.9%)	74 (34.6%)	48 (32.2%)
College graduate	250 (20.5%)	165 (22.7%)	36 (16.8%)	31 (20.8%)
Post-graduate degree	93 (7.6%)	57 (7.8%)	15 (7.0%)	12 (8.1%)
Age distribution				
Mean (SD)	57.9 (15.7)	58.4 (15.0)	56.1 (16.7)	61.2 (16.8)
Median	58	58	56	61
Range	18 – 94	18 – 94	18 – 92	18 – 92

	Evaluators (N=1218)	Verified Uses (N=727)	Rejected from Purchasing (N=214)	Non- Purchasers (N=149)
Age groups				
18-20	13 (1.1%)	3 (0.4%)	2 (0.9%)	3 (2.0%)
21-30	57 (4.7%)	31 (4.3%)	14 (6.5%)	6 (4.0%)
31-40	93 (7.6%)	47 (6.5%)	21 (9.8%)	6 (4.0%)
41-50	217 (17.8%)	134 (18.4%)	42 (19.6%)	21 (14.1%)
51-60	303 (24.9%)	188 (25.9%)	48 (22.4%)	35 (23.5%)
61-70	250 (20.5%)	155 (21.3%)	46 (21.5%)	24 (16.1%)
71-80	190 (15.6%)	112 (15.4%)	20 (9.3%)	39 (26.2%)
81-90	92 (7.6%)	56 (7.7%)	20 (9.3%)	14 (9.4%)
> 90	3 (0.2%)	1 (0.1%)	1 (0.5%)	1 (0.7%)
Age 65 or younger	818 (67.2%)	494 (68.0%)	149 (69.6%)	81 (54.4%)
Age 65 or older	412 (33.8%)	238 (32.7%)	69 (32.2%)	69 (46.3%)
Age 75 or younger	1032 (84.7%)	618 (85.0%)	184 (86.0%)	114 (76.5%)
Age 75 or older	203 (16.7%)	121 (16.6%)	33 (15.4%)	36 (24.2%)
Normal Literacy*	1042 (85.6%)	636 (87.5%)	173 (80.8%)	123 (82.6%)
Low Literacy*	162 (13.3%)	89 (12.2%)	35 (16.4%)	20 (13.4%)
Missing	14 (1.1%)	2 (0.3%)	6 (2.8%)	6 (4.0%)
Abbreviations: GED = general education diploma, SD = standard deviation				
* Normal literacy: subjects scoring at least 61 on the REALM test; low literacy: subjects scoring less than 61 on the REALM test.				
Source: Table 8 of CL2008-13 study report.				

For the actual use study CL2008-13, the Applicant describes label ineligibilities as those symptoms or conditions, included in the proposed OTC label, that consumers may have, but that indicate they should not use the product or that they should seek medical advice. The symptoms or conditions include not meeting the OAB symptom conditions, possible UTI (fever or chills with dysuria, or hematuria, or back or flank pain, or cloudy, foul-smelling urine), stress incontinence only, diagnosis of urinary or gastric retention, narrow-angle glaucoma, or allergy to oxybutynin. Narrow-angle glaucoma and drug allergy were exclusion criteria in the actual use study. The label cautions consumers to speak with their doctor if they have risk factors for diabetes (a history of diabetes in the immediate family, excessive thirst, extreme hunger, or increased tiredness), unexplained weight loss (conservative indicator of bladder cancer risk when reported with dysuria, hematuria, or flank/back pain), liver or kidney disease (including kidney stones), or are using diuretics or other prescription drugs indicated for treatment of OAB. The following table shows the purchase and use decisions of subjects reporting these label ineligibilities in the actual use study CL2008-13.

Table 2: Study CL2008-13 (Actual Use Study) Purchase and Use Decisions by Subjects with Label Ineligibilities^a

	Total Evaluators of Label N=1218 (%) ^b	Purchase Decision = Yes N=1069	Dispensed Drug N=855	Used Drug N=785 (%)	Spoke with Doctor and Used N=181 ^c
< 2 OAB symptoms or < 3 months duration	179 (14.7)	138	103	88 (11.2)	11
Stress incontinence	315 (25.9)	281	214	198 (16.3)	^c
Possible UTI	260 (21.3)	229	166	154 (19.6)	19
Diabetes risk	516 (42.4)	454	351	312 (40.9)	79
Bladder cancer risk	188 (15.4)	163	107	100 (12.7)	12
Diuretic use	152 (12.5)	131	104	98 (12.5)	47
Liver/kidney disease	99 (8.1)	81	67	59 (7.5)	17

	Total Evaluators of Label N=1218 (%) ^b	Purchase Decision = Yes N=1069	Dispensed Drug N=855	Used Drug N=785 (%)	Spoke with Doctor and Used N=181 ^e
Incomplete emptying	522 (42.9)	458	357	323 (41.1)	3
Gastric retention, allergy, and/or narrow angle glaucoma ^d	36 (2.9)	35	21	20 (2.5)	0
Other OAB drug use	176 (14.4)	146	118	110 (14.0)	14

^a Some subjects may be counted more than once if they reported symptoms that met more than one criteria.
^b The total number of label evaluators following enrollment.
^c This data was not reported for all subjects who reported stress incontinence.
^d The label evaluators may have reported more than one condition. All subjects reporting narrow angle glaucoma (n=4) or allergy (n=5) were excluded from the Use phase of the trial. All four subjects reporting narrow angle glaucoma and four of five subjects with allergy wished to purchase the drug.
^e This is the total number of subjects who spoke with their doctor after purchase around the time of their initial use.
Source: Adapted from several Tables within Sections 11.1 and 11.2 of Study CL2008-13 Report.

In summary, in the actual use study CL2008-13, of the 1069 subjects who made an Oxytrol purchase decision, 839 subjects (78.5%) made a positive purchase decision and had ineligibilities according to the label; and only 230 subjects (21.5%) were eligible as per the label.

3.1.4 Primary Efficacy Endpoint

The original primary endpoint was the proportion of subjects who did not stop Oxytrol use when they either developed a new symptom referred to anywhere in the labeling or when their condition worsened, calculated by dividing the total number of subjects in these categories by the total number of subjects that used the Oxytrol patch at least once.

The primary endpoint was amended per the Food and Drug Administration's request to also include subjects who developed symptoms of abdominal and/or pelvic pain. Since abdominal and/or pelvic pain are not referred to anywhere in the Oxytrol labeling, subjects had no way of knowing that if these symptoms occurred that they should discontinue use.

The analysis for the primary endpoint was performed using the analytical methodology as per the statistical analysis plan. Per the analysis, subjects must not have applied another patch once they experienced either an onset of or a worsening of, or the development of a new symptom (as per the label). Comprehensive open-ended data were collected if subjects developed a worsening of their OAB or if they developed new symptoms. It was not feasible to consider this data in the programmatic analysis. However, these data are necessary to have a complete understanding of subjects' behavior and reasoning behind what they did or did not do. Further, this enables a mitigation of the data as described below.

To determine whether consumer behavior was acceptable in subjects who were classified as Oxytrol misusers, a mitigation assessment of the primary endpoint was conducted post-hoc by a panel of three independent physicians (2 urologists and an urogynecologist) and one physician employed by the Sponsor. Each physician evaluated whether it was acceptable for the subject to have continued using the product. If there was consensus among the physicians and the decision followed the guidelines that the subject's actions were medically acceptable, the subject's misuse

was considered to be mitigated. According to the clinical reviewer, most of the mitigation seems reasonable. Please refer to the clinical review for more detailed discussion of the mitigation.

Table 3: Study CL2008-13 Primary Endpoint - The Proportion of Subjects Who Did Not Stop Use When They Either Developed a New Symptom Referred to Anywhere in the Labeling or When Their Condition Worsened Including Abdominal and/or Pelvic Pain - Users

Primary Endpoint	Pre-mitigation (N=727) ^a	Post-mitigation (N=727) ^a
Total subjects who had no new symptoms indicating they should stop use	586 (80.6%)	586 (80.6%)
Total subjects who had symptoms indicating they should stop use	141 (19.4%)	141 (19.4%)
Total subjects who correctly stopped use (pre-mitigation) or were medically acceptable (post-mitigation):	36 (5.0%)	116 (16.0%)
Developed a new symptom only	28 (3.9%)	88 (12.1%)
Condition worsened only	4 (0.6%)	15 (2.1%)
Developed new symptom and condition worsened	4 (0.6%)	13 (1.8%)
Total subjects who failed to stop use:	105 (14.4%)	25 (3.4%)
Developed a new symptom only	73 (10.0%)	13 (1.8%)
Condition worsened only	22 (3.0%)	11 (1.5%)
Developed new symptom and condition worsened	10 (1.4%)	1 (0.1%)
Total subjects who failed to stop use	105 (14.4%)	25 (3.4%)
95% CI (LL, UL)	(12.0%, 17.2%)	(2.2%, 5.0%)
Abbreviations: CI = confidence interval, LL = lower bound, UL = Upper bound.		
^a Includes N=12 subjects presenting with complaints of abdominal or pelvic pain only (includes subjects who mentioned abdominal and pelvic pain in narratives of potentially related adverse experiences.		
^b Exact confidence interval.		
Source: Table 13 of CL2008-13 Study report.		

Pre-mitigation the proportion of subjects who did not stop use when they either developed a new symptom or when their condition worsened was 105/727 users (14.4%, 95% CI: 12.0%, 17.2%). Post mitigation, the number was reduced to 25/727 users (3.4%, 95% CI: 2.2%, 5.0%) because 80/105 subjects who were programmatically misusers demonstrated medically acceptable behavior.

Table 4: Study CL2008-13 Primary Endpoint Subgroup - The Proportion of Subjects Who Did Not Stop Use When They Either Developed a New Symptom Referred to Anywhere in the Labeling or When Their Condition Worsened Including Abdominal and/or Pelvic Pain - Users

Primary Endpoint	Pre-Mitigation (N=141) ^a	Post-Mitigation (N=141)
Total subjects who correctly stopped use (pre-mitigation) or were medically acceptable (post-mitigation)	36 (25.5%)	116 (82.3%)
Developed a new symptom only	28 (19.9%)	88 (62.4%)
Condition worsened only	4 (2.8%)	15 (10.6%)
Developed new symptom and condition worsened	4 (2.8%)	13 (9.2%)
Total subjects who failed to stop use	105 (74.5%)	25 (17.7%)
Developed a new symptom only	73 (51.8%)	13 (9.2%)
Condition worsened only	22 (15.6%)	11 (7.8%)
Developed new symptom and condition worsened	10 (7.1%)	1 (0.7%)
Total subjects who failed to stop use	105 (74.5%)	25 (17.7%)
95% CI (LL, UL) ^b	(66.4%, 81.4%)	(11.8%, 25.1%)
Abbreviations: CI = confidence interval, LL = lower bound, UL = Upper bound.		
^a Includes N=12 subjects presenting with complaints of abdominal or pelvic pain only (includes subjects who mentioned abdominal and pelvic pain in narratives of potentially related adverse experiences.		
^b Exact confidence interval.		
Source: Table 14 of CL2008-13 Study report.		

As seen in the above table, of the 141 subjects who had symptoms, indicating they should stop using Oxytrol, 74.5% (105/141) of subjects failed to stop use based on the pre-mitigation assessment and 17.7% (25/141) of subjects failed to stop use based on the postmitigation assessment.

Statistical Reviewer’s Comments:

The upper bound (5%) of the confidence interval for the proportion of subjects who did not stop use when they either developed a new symptom referred to anywhere in the labeling or when their condition worsened including abdominal and/or pelvic pain meets the pre-defined target threshold of 5%.

3.1.5 Selected Secondary Endpoints

As noted in Section 3.1.2, there were a total of 5 secondary endpoints evaluated by the Applicant. In this Section, the statistical reviewer will focus on study results for 2 of these 5 secondary endpoints: secondary endpoints 3, and 5.

3.1.5.1 Secondary Endpoint 3

Secondary Endpoint 3 was the proportion of subjects who did not stop using Oxytrol within two weeks after experiencing no improvement in their symptoms. In order for a subject to have met the criteria for correctly stopping use, she had to have stated that her symptoms stayed the same or worsened at the follow-up Week 3 visit and, her diary must have reflected that she used the patch for 14 days or less. Among the 727 users, there were 643 subjects used the product for a full 2 weeks.

Table 5: Study CL2008-13 Secondary Endpoint 3 - The Proportion of Users Who Did Not Stop Use Within 2 Weeks after No Improvement - Users

Secondary Endpoint 3	All Subjects Pre-Mitigation	All Subjects Post-Mitigation
Total subjects asked the question at least 2 weeks after their first application ^b	643	643
Subjects reporting improvement	456 (70.9%)	456 (70.9%)
Subjects reporting no improvement (stayed the same or worsened)	187 (29.1%)	187 (29.1%)
Total subjects with no improvement who correctly stopped use	42 (6.5%)	116 (18.0%)
Total subjects with no improvement who failed to stop use	145 (22.6%)	71 (11.0%)
95% CI (LL, UL) ^b	(19.4%, 26.0%)	(8.7%, 13.7%)
^a Of the N=727 subjects in the User Population, N=690 had used the product by the date of the first follow-up interview and N=643 had been using the product for a full 2-weeks. ^b Exact confidence intervals. Source: Table 18 of CL2008-13 study report.		

3.1.5.2 Combined Primary and Secondary Endpoint 3

Per the FDA's request, an analysis combining the Primary Endpoint and Secondary Endpoint 3 was conducted. It shows the proportion of subjects who did not stop use when they either developed a new symptom referred to anywhere in the labeling or when their condition did not improve (worsened or stayed the same) with the addition of abdominal and pelvic pain.

The combined data for the Primary Endpoint and Secondary Endpoint 3 are shown in the following table. In the User Population of 727 subjects, the total number of subjects who failed to stop using Oxytrol when they either developed a new symptom referred to in the labeling or when their condition did not improve was 219 (30.1%; 95% CI: 26.8%, 33.6%) pre-mitigation and 89 (12.2%; 95% CI: 9.9%, 14.8%) post-mitigation.

Table 6: Study CL2008-13 Combined Primary Endpoint and Secondary Endpoint 3: The Proportion of Subjects Who Did Not Stop Use When They Either Developed a New Symptom Referred to Anywhere in the Labeling or When Their Condition Did Not Improve (Worsened or Stayed the Same) With the Addition of Abdominal and Pelvic Pain – Users

Primary Endpoint Combined with Secondary Endpoint 3^a	Pre-Mitigation (N=727)^{a,b}	Post-Mitigation (N=727)^a
Total subjects who met either the criteria of the Primary Endpoint or Secondary Endpoint 3^c	276 (38.0%)	Not applicable
Developed a new symptom	115 (15.8%)	Not applicable
OAB condition worsened	40 (5.5%)	Not applicable
OAB condition stayed the same at Follow-up Visit 3	174 (23.9%)	Not applicable
Total subjects who correctly stopped use (pre-mitigation) or were medically acceptable (post-mitigation)^c	57 (7.8%)	187 (25.7%)
Developed a new symptom	27 (3.7%)	93 (12.8%)
OAB condition worsened	8 (1.1%)	25 (3.4%)
OAB condition stayed the same at Follow-up Visit 3	34 (4.7%)	105 (14.4%)
Total subjects who failed to stop use^c	219 (30.1%)	89 (12.2%)
Developed a new symptom	88 (12.1%)	22 (3.0%)
OAB condition worsened	32 (4.4%)	15 (2.1%)
OAB condition stayed the same at Follow-up Visit 3	140 (19.3%)	69 (9.5%)
Total subjects who failed to stop use	219 (30.1%)	89 (12.2%)
95% CI (LL, UL) ^d	(26.8%, 33.6%)	(9.9%, 14.8%)
<p>^a For Secondary Endpoint 3 (SE3), users who did not stop use within 2-weeks after no improvement (stayed the same or worsened) analysis only includes subjects who were asked the question about improvement at least 2-weeks after their first application. Of the N=727 subjects in the User Population, N=690 had used the product by the date of the first follow-up interview and N=643 had been using the product for a full 2-weeks.</p> <p>^b Includes N=12 subjects only presenting with complaints of abdominal or pelvic pain (includes subjects who mentioned abdominal and pelvic pain in narratives of potentially related adverse experiences).</p> <p>^c Subjects are counted either as meeting the criteria of both the PE and SE3 or not meeting one of the endpoints. Under each group the subject will be counted in the row of each specific criterion. Counts of subjects who met or did not meet the specific criteria shown above will not match the counts displayed in the individual endpoint tables since a subject might have met one endpoint but not the other. In addition, a mitigation assessment for the PE will take priority if a subject does not meet the criteria for both endpoints. Note: One subject, who is counted in the total counts of misusers, is not included in any specific row because she was incorrect for all three criteria.</p> <p>^d Exact confidence intervals.</p>		
Source: Table 20 of CL2008-13 study report.		

3.1.5.3 Secondary Endpoint 5

Secondary Endpoint 5 is the Proportion of subjects who misused the patch (incorrect duration of use > 4 days or simultaneous use). Secondary Endpoint 5 was analyzed based on pre- and post-mitigation assessments but the post-mitigation analysis includes all subject data and is a better reflection of the subject's overall behavior.

The following table presents the proportion of subjects who misused the Oxytrol patch. Of the subjects who incorrectly used the patch, more favorable results were seen when the data were

analyzed post-mitigation versus pre-mitigation (21.2%; 95% CI: 18.3%, 24.4% versus 51.7%; 95% CI 47.9%, 55.4%). When evaluating the data post-mitigation, the majority of subjects correctly used (≤ 4 days and no simultaneous use) the Oxytrol patch (78.8%; 95% CI: 75.6%, 81.7%).

Table 7: Study CL2008-13 Proportion of Subjects Who Misused the Patch (Incorrect Duration of Use and/or Simultaneous Use) – Users

Secondary Endpoint 5	Patches Used (N=7874) ^a	Total Subjects Pre-Mitigation (N=727) ^a	Total Subjects Post-Mitigation (N=727) ^{a,b}
Incorrect use (> 4 days or simultaneous use)	1180 (15.0%)	370 (51.7%)	152 (21.2%)
95% CI (LL, UL) ^b	(14.2%, 15.8%)	(47.9%, 55.4%)	(18.3%, 24.4%)
Correct use (≤ 4 days, no simultaneous use)	6694 (84.9%)	346 (48.3%)	564 (78.8%)
95% CI (LL, UL) ^b	(84.1%, 85.7%)	(44.6%, 52.1%)	(75.6%, 81.7%)
^a Some subjects with verified use had missing patch use entries.			
^b Exact confidence intervals.			
Source: Table 40 of CL2008-13 study report.			

3.1.6 Subgroup Analyses Based on Age Category

The following table summarizes the post-mitigation primary endpoint (the proportion of subjects who did not stop use when they either developed a new symptom referred to anywhere in the labeling or when their condition worsened including abdominal and/or pelvic pain) based on age category (women less than 65 years old vs. women 65 years or older).

Table 8: Study CL2008-13 Post-Mitigation Primary Endpoint – Statistical Reviewer’s Analysis Based on Age Category (less than 65 years vs. 65 years or older)

Primary Endpoint	Subjects less than 65 years old (N=489) ^a	Subjects 65 years or older (N=238) ^a
Total subjects who had no new symptoms indicating they should stop use	406 (83.0%)	180 (75.6%)
Total subjects who had symptoms indicating they should stop use	83 (17.0%)	58 (24.4%)
Total subjects who failed to stop use	14 (2.9%)	11 (4.6%)
95% CI (LL, UL) ^b	(1.6%, 4.8%)	(2.3%, 8.1%)
Abbreviations: CI = confidence interval, LL = lower bound, UL = Upper bound.		
^a Includes subjects presenting with complaints of abdominal or pelvic pain only (includes subjects who mentioned abdominal and pelvic pain in narratives of potentially related adverse experiences.		
^b Exact confidence interval.		

The following table summarizes the post-mitigation secondary endpoint 3 (the proportion of users who did not stop use within 2 weeks after no improvement) based on age category (women less than 65 years old vs. women 65 years or older).

Table 9: Study CL2008-13 Post-Mitigation Secondary Endpoint 3 – Statistical Reviewer’s Analysis Based on Age Category (less than 65 years vs. 65 years or older)

Secondary Endpoint 3	Subjects less than 65 years old	Subjects 65 years or older
Total subjects asked the question at least 2 weeks after their first application^a	431	212
Subjects reporting improvement	318 (73.8%)	138 (65.1%)
Subjects reporting no improvement (stayed the same or worsened)	113 (26.2%)	74 (34.9%)
Total subjects with no improvement who failed to stop	42 (9.7%)	29 (13.7%)
95% CI (LL, UL) ^b	(7.1%, 12.9%)	(9.4%, 19.1%)
Abbreviations: CI = confidence interval, LL = lower bound, UL = Upper bound.		
^a For Secondary Endpoint 3 (SE3), users who did not stop use within 2-weeks after no improvement (stayed the same or worsened) analysis only includes subjects who were asked the question about improvement at least 2-weeks after their first application. Of the N=727 subjects in the User Population, N=690 had used the product by the date of the first follow-up interview and N=643 had been using the product for a full 2-weeks.		
^b Exact confidence interval.		

From the above subgroup analyses results based on age category for both primary and secondary endpoint 3, although subjects 65 years or older had higher misuse rates for both endpoints, it seems that the misuse rates are compatible between the two age groups because the 95% CIs for the misuse rate point estimates of these two age groups overlap with each other.

3.2 Pivotal Label Comprehension Study (Study Protocol 10053)

For all the label comprehension and self-selection studies’ results, the Applicant only provided the lower bound of the 95% CI without the upper bound; the statistical reviewer calculated and presented most of the 95% CI with both upper bound and lower bound.

3.2.1 Study Design

This was a multi-site, single visit label comprehension study among a population of female respondents who self-reported OAB symptoms or diabetes risk factors.

This study was designed to evaluate consumers' ability to comprehend the Oxytrol label including the “uses” and “warnings” among a general population of women who self-report OAB symptoms or who self-report diabetes risk factors.

For this label comprehension study, three cohorts of females were evaluated. The general population (Cohort 1) consisted of females with OAB symptoms, an enriched sample of low literacy females with OAB symptoms comprised Cohort 2, and a targeted population of females 44+ who self-reported diabetes risk factors made up Cohort 3.

This study was conducted in a population of women who self-reported OAB symptoms or diabetes risk factors. The stimulus used in the study was a full mock-up package. The

respondent's visit consisted of a review of the product label, just as they would in a real-life setting when first approaching the product on the shelf, and the labeling remained available to the respondent at all times during the interview.

During the interview, Cohort 1 and 2 respondents were asked fifteen (15) comprehension questions and Cohort 3 subjects were asked six (6) comprehension questions regarding the primary communication objectives. The label comprehension questions were comprised of scenario-based and open-ended questions. Following each comprehension question, all respondents were asked a follow-up question (“*Why do you say that?*”) to better understand the rationale for their initial response. Responses, including the respondent's verbatim responses, were documented. Subjects in Cohort 1 and 2 received a different version of the questionnaire than those subjects in Cohort 3.

3.2.2 Statistical Methodologies

Efficacy Endpoints

The primary endpoint for this study is the number of subjects who have a correct overall response for each primary communication objective.

All primary objectives for Cohort 1 will be categorized based on high versus low medical consequence. Risk classifications are as follows:

- Higher Medical Consequences
 - Have urinary retention (are 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
 - If allergic to oxybutynin
 - You have an allergic reaction to this product
 - You have severe redness, itchiness or blistering at the site of application

- Lower Medical Consequences
 - You may be suffering from overactive bladder if you have had 2 or more of the following symptoms for the 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)
 - 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)

Primary Analysis

Cohort 1

The primary statistical analysis will consist of point estimates for the proportion of general consumers (Cohort 1) who have successfully met the primary communication objective and the corresponding lower two-sided 95% exact confidence bounds. The rate was computed as the number of subjects with an overall correct response divided by the number of subjects in the general population who answered the question. The lower bound of two-sided 95% confidence limits was computed using the exact method.

The primary endpoint would have met the target threshold if the lower limit of the two-sided 95% exact confidence interval for general population is above 90% for higher medical consequence objectives and is above 85% for lower medical consequence objectives.

Cohort 3

The primary endpoint for this study was the number of female subjects with diabetes risk factors who had a correct overall response for the primary communication objectives. The primary analysis consisted of estimating the correct comprehension rate for this targeted group. The rate was computed as the number of subjects with an overall correct response divided by the number of subjects in Cohort 3 who answered the question. The lower bound of a two-sided 95% confidence limit was computed using the exact method. If the lower confidence limit was at least 85%, it was concluded that the objective was comprehended.

Determination of Sample Size

Cohort 1

In order to calculate the sample sizes, consideration was given for the target comprehension threshold which was set at a lower bound of 90% for the primary objectives with higher medical consequence and 85% for the primary objectives with lower medical consequence. In addition, consideration was given to the overall power of the study. The sample size target for the main cell was targeted to be 500 subjects. This sample size provides 92% power to conclude that the true comprehension rate for the objectives of lower medical consequence is at least 85% when the observed comprehension rate is 90% or higher, based on a two-sided exact test at the 5% level. The objectives of higher medical consequence had to meet a more stringent test. The target sample size of 500 provides a 92% power to conclude that the true comprehension rate is at least 90% when the observed comprehension rate is 94.5% or higher, based on a two-sided exact test at the 5% level.

Cohort 2

A sample size of 150 subjects in the Low Literacy cohort is intended to allow for review of data for this group but it is not powered to meet the target threshold.

Cohort 3

In order to calculate the sample sizes, consideration was given for the target comprehension threshold which was set at a lower bound of 85% for the primary objectives. The concern about undiagnosed diabetes was considered to be a lower medical risk, since diabetes is a condition with numerous and varied symptoms which typically progresses slowly. A diabetic consumer without OAB who tries the oxybutynin patch will not experience relief for the symptoms which are caused by diabetes. In addition, consideration was given to the overall power of the study. The sample size target for Cohort 3 was 150. This sample size provides 80% power to conclude that the true comprehension rate for the objectives of lower medical consequence is at least 85% when the observed comprehension rate is 90% or higher, based on a two-sided exact test at the 5% level.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Cohort 1 and 2

All five hundred ninety-two (592) Cohort 1 and 2 respondents completed the study. Within the general population, the majority of respondents were Caucasian (n=360, 76.3 %) and had at least some college or technical school (n=336, 71.2%). The low literacy subgroup differed substantially from the GP cohort on several demographic characteristics, notably race, education and income.

Table 10: Study 10053 Cohort 1 and 2 Baseline Characteristics

		GP Women With Urinary Symptoms (N=472)		†LL Women with Urinary Symptoms (N=152)	
Age		n	%	n	%
	18 to 24	27	5.7	26	17.1
	25 to 34	61	12.9	31	20.4
	35 to 43	92	19.5	41	27.0
	44 to 49	64	13.6	25	16.4
	50 to 54	43	9.1	10	6.6
	55 to 59	40	8.5	9	5.9
	60 to 64	43	9.1	4	2.6
	65 to 69	65	13.8	2	1.3
	70 or above	37	7.8	4	2.6
Race					
	Caucasian/White	360	76.3	27	17.8
	African American/Black	83	17.6	107	70.4
	Native American	3	0.6	5	3.3
Race					
	Hispanic	15	3.2	8	5.3
	Asian	4	0.8	4	2.6
	Other	7	1.5	1	0.7
Education					
	Less than High School	16	3.4	66	43.4
	Completed High School	120	25.4	52	34.2

		GP Women With Urinary Symptoms (N=472)		†LL Women with Urinary Symptoms (N=152)	
Education	Some College/Technical School	196	41.5	33	21.7
	Graduated College / Technical School or more	140	29.7	1	0.7
Income	\$0 to \$14,999	50	10.6	92	60.5
	\$15,000 to \$24,999	73	15.5	23	15.1
	\$25,000 to \$34,999	72	15.3	13	8.6
	\$35,000 to \$44,999	66	14.0	16	10.5
	\$45,000 to \$64,999	79	16.7	6	3.9
	\$65,000 to \$74,999	35	7.4	--	--
	\$75,000 or more	85	18.0	2	1.3
	Refused	12	2.5	--	--
Literacy	Normal Literacy	440	93.2		
	Low Literacy	32	6.8	152	100.0
REALM	MEAN	64.2		54.2	
	SD	3.3		7.1	
	MEDIAN	65		57	
	RANGE	38 to 66		20 to 60	
†Includes low literacy respondents from the General Population (n=32) as well as the additional enriched low literacy completes (n=120) Source: Table 5 of Study 10053 Report, with the REALM statistics calculated by the statistical reviewer.					

3.2.3.2 Cohort 3

All one hundred sixty (160) Cohort 3 respondents completed the study. Within Cohort 3, a large subgroup of respondents were over 60 years old (n=64; 40.0%), were Caucasian (n=109, 68.1%), and had at least some college or technical school (n=108, 67.5%). Specific demographic breakdowns are illustrated in the following table.

Table 11: Study 10053 Cohort 3 Baseline Characteristics

		Target Population Women with Diabetes Risk Factors (N=160)	
Age		n	%
	44 to 49	43	26.9
	50 to 54	28	17.5
	55 to 59	25	15.6
	60 to 64	28	17.5
	65 to 69	23	14.4
Age	70 or above	13	8.1
Race	Caucasian/White	109	68.1
	African American/Black	45	28.1
	Native American	2	1.3

		Target Population Women with Diabetes Risk Factors (N=160)	
Race	Hispanic	1	0.6
	Asian	2	1.3
	Other	1	0.6
Education	Less than High School	7	4.4
	Completed High School	45	28.1
	Some College/Technical School	55	34.4
	Graduated College / Technical School or more	53	33.1
Income	\$0 to \$14,999	21	13.1
	\$15,000 to \$24,999	27	16.9
	\$25,000 to \$34,999	22	13.8
	\$35,000 to \$44,999	20	12.5
	\$45,000 to \$64,999	29	18.1
	\$65,000 to \$74,999	12	7.5
	\$75,000 or more	26	16.3
	Refused	3	1.9
Literacy	Normal Literacy	142	88.8
	Low Literacy	18	11.3
REALM	MEAN	63.1	
	SD	6.1	
	MEDIAN	65	
	RANGE	26 to 66	

Source: Table 27 of Study 10053 Report, with the REALM statistics calculated by the statistical reviewer.

3.2.4 Results and Conclusion

3.2.4.1 Cohort 1 and 2

As shown in the following table, two of the six primary communication objectives of higher medical consequence met the threshold. Of the remaining four objectives, one objective, “Not Okay – Has Narrow-angle Glaucoma” missed the lower bound threshold by more than five percentage points.

Table 12: Study 10053 Analysis of Primary Communication Objectives – Higher Medical Consequence

Total Responding	General Population N = 472		Normal Literate Women ¹ N = 440		† Low Literate Women N=152	
	n	% (95% CI ²)	n	% (95% CI ²)	n	% (95% CI ²)
Card I: Not okay, has narrow angle glaucoma (Q9)						
<u>Demonstrate Comprehension</u>	414	87.7% (84.4%, 90.5%)	397	90.2% (87.1%, 92.8%)	113	74.3% (66.6%, 81.1%)

Total Responding	General Population N = 472		Normal Literate Women ¹ N = 440		† Low Literate Women N=152	
	n	% (95% CI ²)	n	% (95% CI ²)	n	% (95% CI ²)
Card J: Stop use and ask a doctor, developed blisters and red and itchy (Q10) <u>Demonstrate Comprehension</u>	418	88.6% (85.3%, 91.3%)	391	88.9% (85.6%, 91.7%)	134	88.2% (81.9%, 92.8%)
Card K: Not okay, has gastric retention (Q11) <u>Demonstrate Comprehension</u>	424	89.8% (86.7%, 92.4%)	400	90.9% (87.8%, 93.4%)	113	74.3% (66.6%, 81.1%)
Card L: Not Okay, allergic to oxybutinin (Q12) <u>Demonstrate Comprehension</u>	449	95.1% (92.8%, 96.9%)	422	95.9% (93.6%, 97.6%)	137	90.1% (84.2%, 94.4%)
Card N: Not okay, has urinary retention (Q14) <u>Demonstrate Comprehension</u>	431	91.3% (88.4%, 93.7%)	408	92.7% (89.9%, 95.0%)	124	81.6% (74.5%, 87.4%)
Card O: Stop use and ask a doctor, allergic reaction (Q15) <u>Demonstrate Comprehension</u>	440	93.2% (90.6%, 95.3%)	409	93.0% (90.2%, 95.2%)	140	92.1% (86.6%, 95.9%)
† Includes low literacy respondents from the General Population (n=32) as well as the additional enriched low literacy completes (n=120) ¹ Normal literacy estimates were calculated by the statistical reviewer. ² CI is based on exact confidence limit. Source: Table 6, 7, and 8 of Study 10053 Report. However, the upper bounds of the CI were calculated by the statistical reviewer since they were not included in the Applicant's submission.						

The following table demonstrates that one (1) of the five (5) primary objectives with lower medical consequence met the established 85% lower bound threshold. Of the remaining four objectives, “Not Okay – Stress Incontinence” missed the lower bound threshold by more than 5 percentage points.

Table 13: Study 10053 Analysis of Primary Communication Objectives – Lower Medical Consequence

Total Responding	General Population N = 472		Normal Literacy ¹ N = 440		† Low Literacy N = 152	
	n	% (95% CI ²)	n	% (95% CI ²)	n	% (95% CI ²)
Card D: Ask a doctor, kidney stones (Q4) <u>Demonstrate Comprehension</u>	424	89.8% (86.7%, 92.4%)	398	90.5% (87.3%, 93.0%)	135	88.8% (82.7%, 93.9%)
Card E: Not okay, stress incontinence (Q5) <u>Demonstrate Comprehension</u>	365	77.3% (73.3%, 81.0%)	350	79.6% (75.5%, 83.2%)	91	59.9% (51.6%, 67.7%)
Card F: Have symptoms of OAB for at least 3 months (Q6) <u>Demonstrate Comprehension</u>	412	87.3% (83.9%, 90.2%)	387	88.0% (84.5%, 90.9%)	108	71.1% (63.2%,
Card G: Ask a doctor /pharmacist, using diuretic (Q7) <u>Demonstrate Comprehension</u>	411	87.1% (83.7%, 90.0%)	384	87.3% (83.8%, 90.2%)	131	86.2% (79.7%, 91.2%)

Total Responding	General Population N = 472		Normal Literacy ¹ N = 440		† Low Literacy N = 152	
	n	% (95% CI ²)	n	% (95% CI ²)	n	% (95% CI ²)
Card M: Ask a doctor, has liver disease (Q13) <u>Demonstrate Comprehension</u>	396	83.9% (80.3%, 87.1%)	372	84.6% (80.8%, 87.8%)	132	86.8% (80.4%, 91.8%)
† Includes low literacy respondents from the General Population (n=32) as well as the additional enriched low literacy completes (n=120) ¹ Normal literacy estimates were calculated by the statistical reviewer. ² CI is based on exact confidence limit. Source: Table 14, 15, and 16 of Study 10053 Report. However, the upper bounds of the CI were calculated by the statistical reviewer since they were not included in the Applicant's submission.						

3.2.4.2 Cohort 3

Primary Analysis – Ask a Doctor before Use if Family History of Diabetes

One of the primary objectives of Cohort 3 (females who have a history of diabetes risk factors) was to evaluate the subjects' ability to understand that a doctor should be consulted prior to use if a history of diabetes is present in their immediate family.

Another primary objective of this study was to evaluate the subject's ability to understand the diabetes warning, "Ask a doctor before use if you have frequent urination with excessive thirst, extreme hunger, or increased tiredness. These could be early signs of diabetes."

The results for these two primary objectives are listed in the following table.

Table 14: Study 10053 Analysis of Family History of Diabetes Warning and Frequent Urination with Excessive Thirst for Cohort 3

Total Responding	Females 44 +, with Diabetes Risk Factors (n=160)	
	n	% (95% CI ¹)
Family History of Diabetes <u>Demonstrate Comprehension</u>	142	88.8% (82.8%, 93.2%)
Frequent Urination with Excessive Thirst <u>Demonstrate Comprehension</u>	141	88.1% (82.1%, 92.7%)
¹ CI is based on exact confidence limit. Source: Table 28 and 32 of Study 10053 Report. However, the upper bounds of the CI were calculated by the statistical reviewer since they were not included in the Applicant's submission.		

4 Other Label Comprehension Studies

For all the label comprehension and self-selection studies' results, the Applicant only provided the lower bound of the 95% CI without the upper bound; the statistical reviewer calculated and presented most of the 95% CI with both upper bound and lower bound.

4.1 Targeted Label Comprehension Study of Diabetes Warnings (Protocol #92099)

This quantitative, targeted label comprehension study was designed to assess whether women are able to comprehend the diabetes warnings which state that they should consult a physician before use if there is a possibility of diabetes including family history or potential diabetic symptoms.

The proposed labeling for Oxytrol includes specific information regarding diabetes including:

- The Drug Facts include a message that indicates [REDACTED] (b) (4)
- The Drug Facts also include a message that indicates [REDACTED] (b) (4)
- A Warning indicates that [REDACTED] (b) (4)

Two (2) cohorts of females were evaluated in this study; general population and an augment sample of low literacy. The target population consisted of females suffering from OAB symptoms ages 18 years or older. This population was recruited using site databases.

The primary objective of this study was to evaluate comprehension of the enhanced Oxytrol diabetes warning by females suffering from OAB symptoms:

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

The primary endpoint for this study was the number of general population subjects who have a correct overall response for the primary communication objective regarding the diabetes warnings.

The primary analysis consists of estimating the correct comprehension rate for the general population (Cohort 1). The rate was computed as the number of subjects with an overall correct response divided by the number of subjects in the general population who answered the question. The lower bound of two-sided 95% confidence limit was computed using the exact method. If the lower confidence limit was at least 90%, it was concluded that the objective was comprehended.

A sample of 350 respondents in the general population cohort provides 92% power to conclude that the true comprehension rate for the primary objective is at least 90% when the observed comprehension rate is 95% or higher, based on a two-sided exact test at the 5% level. A sample size of 250 respondents in the augmented low literacy cohort provides 80% power to conclude that the true comprehension rate for the primary objective is at least 90% when the observed comprehension rate is 95% or higher, based on a two-sided exact test at the 5% level.

The study recruited 590 subjects, and all five hundred ninety (590) respondents completed the study. For the total study population (n=590), age ranges were comprised of a slightly older population, consistent with those who suffer from OAB symptoms. Ages ranged from 18-29 (13.4%), 30-40 (16.4%), 41-49 (23.9%), 50-59 (27.1%) and 60 or older (19.2%). For the general population cohort, the majority of respondents were Caucasian (n=301, 83.6 %) followed by African- American (n=51, 14.2%). A total of 3.6% (n=13) of respondents were Hispanic. Most respondents had some college/technical school (n=153, 42.5%), or graduated college/technical school or more (n=116, 32.2%) or and income ranges were evenly dispersed. The demographics and other characteristics of the respondents completing this study are included below in the following table.

Table 15: Study 92099 Respondents' Gender, Age, Race, Ethnicity, Education, and Income

	Total (N=590)		GP Females with OAB Symptoms, Age 18 + (N=360)		† LL Women with OAB Symptoms, Age 18 + (N=258)	
	n	%	n	%	n	%
Age						
18 to 24	41	6.9	11	3.1	31	12.0
25 to 29	38	6.4	13	3.6	26	10.1
30 to 34	34	5.8	15	4.2	20	7.8
35 to 40	63	10.7	32	8.9	33	12.8
41 to 44	53	9.0	29	8.1	27	10.5
45 to 49	88	14.9	49	13.6	44	17.1
50 to 54	85	14.4	65	18.1	26	10.1
55 to 59	75	12.7	59	16.4	18	7.0
60 to 64	55	9.3	45	12.5	14	5.4
65 or above	58	9.8	42	11.7	19	7.4
Race						
Caucasian/White	363	61.5	301	83.6	82	31.8
African American/Black	202	34.2	51	14.2	159	61.6
Native American	1	0.2	--	--	1	0.4
Other	24	4.1	8	2.2	16	6.2
Education						
Less than High School	86	14.6	4	1.1	83	32.2
Completed High School	215	36.4	87	24.2	137	53.1
Some College/Technical School	167	28.3	153	42.5	27	10.5

		Total (N=590)		GP Females with OAB Symptoms, Age 18 + (N=360)		† LL Women with OAB Symptoms, Age 18 + (N=258)	
		n	%	n	%	n	%
Education	Graduated College / Technical School or more	122	20.7	116	32.2	11	4.3
Income	\$0 to \$14,999	157	26.6	21	5.8	139	53.9
	\$15,000 to \$24,999	98	16.6	40	11.1	69	26.7
	\$25,000 to \$34,999	68	11.5	51	14.2	20	7.8
	\$35,000 to \$44,999	58	9.8	53	14.7	8	3.1
	\$45,000 to \$64,999	88	14.9	82	22.8	9	3.5
	\$65,000 to \$74,999	39	6.6	37	10.3	3	1.2
	\$75,000 or more	71	12.0	70	19.4	3	1.2
	Refused	11	1.9	6	1.7	7	2.7

†Includes low literacy respondents from the General Population (n=28) as well as the additional enriched low literacy completes (n=230)
Source: Table 5 of Study 92099 Report.

One of the primary objectives of this study was to evaluate the subject's ability to understand that a doctor should be consulted prior to use if a history of diabetes is present in the immediate family.

The comprehension results for this primary communication objective appear in the following table and are presented for both the GP cohort and LL respondents. General Population comprehension scores were 92.8% (n=334, LCI=89.6%). Low Literacy respondents scores were somewhat lower at 79.1% (n=204, LCI=73.6%).

Another primary objective of this study was to evaluate the subject's ability to understand the diabetes warning, (b) (4)

Demonstrated comprehension was determined based on the combination of the closed-end and open-end questions. The comprehension results for this primary communication objective appear in the following table and are presented for both the GP cohort and LL respondents. General Population comprehension scores were 94.4% (n=340, LCI=91.6%). Low Literacy respondents' scores were somewhat lower at 70.5% (n=182, LCI=64.6%).

Table 16: Study 92099 Analysis of Family History of Diabetes Warning and Ask a Doctor – Frequent Urination with Excessive Thirst

Total Responding	GP Females 18 +, with OAB Symptoms (N=360)		NL Women with OAB Symptoms, Age 18 + ¹ (N=332)		† LL Women with OAB Symptoms, Age 18 + (N=258)	
	n	% (95% CI ²)	n	% (95% CI ²)	n	% (95% CI ²)
Family History of Diabetes Warning						
<u>Demonstrate Comprehension</u>	334	92.8% (89.6%, 95.2%)	310	93.4% (90.1%, 95.8%)	204	79.1% (73.6%, 83.9%)
Ask a Doctor – Frequent Urination with Excessive Thirst						
<u>Demonstrate Comprehension</u>	340	94.4% (91.6%, 96.6%)	316	95.2% (92.3%, 97.2%)	182	70.5% (64.6%, 76.0%)

Abbreviation: NL = Normal Literacy, LL = Low Literacy

† Includes low literacy respondents from the General Population (n=32) as well as the additional enriched low literacy completes (n=120)

¹ Normal literacy estimates were calculated by the statistical reviewer.

² CI is based on exact confidence limit.

Source: Table 6 and 13 of Study 92099 Report. However, the upper bounds of the CI were calculated by the statistical reviewer since they were not included in the Applicant's submission.

4.2 Targeted Label Comprehension Study of Enhanced Pregnancy Warning (Protocol #92062)

This targeted label comprehension study was designed to assess whether women are able to comprehend the enhanced warning which states that they should consult a physician before use if there is a possibility of pregnancy. The proposed labeling for Oxytrol includes explicit text indicating that frequent urination is an early sign of pregnancy:

- The warning indicates that [REDACTED] (b) (4)
- The Drug Facts also include the codified warning that indicates “If pregnant or breastfeeding, ask a health professional before use.”

Two (2) cohorts of females were evaluated in this study; general population and an augmented sample of low literacy. The target population consisted of females of childbearing age (18-40) who had not been surgically sterilized. This population was recruited using site databases. The primary objective of this study was to evaluate comprehension of the enhanced Oxytrol pregnancy warning by females of childbearing potential:

[REDACTED] (b) (4)

A total of 574 respondents were recruited and interviewed at nine (9) market research facilities geographically dispersed throughout the United States. All five hundred seventy-four (574) respondents completed the study. For the total study population (n=574), age ranges were comprised of a slightly younger population, consistent with those who are of childbearing potential. Ages ranged from 18-24: n=236, 41.1%; 25-29: n=109, 19.0%; 30-34: n=81, 14.1%; 35-40: n=148, 25.8%. For the general population cohort, the majority of respondents were Caucasian (n=243, 69.4 %) followed by African-American (n=62, 17.7%) and other (n=37, 10.6%). A total of 10% (n=35) of respondents were Hispanic. Most respondents had completed a high school education (n=126, 36.0%) or had some college/technical school (n=131, 37.4%), and income ranges were evenly dispersed. The demographics and other characteristics of the respondents completing this study are included below in the following table.

Table 17: Study 92062 Responders' Gender, Age, Race, Ethnicity, Education, and Income

	Total (N=574)		GP Females of Childbearing Age (N=350)		† LL Females of Childbearing Age (N=252)	
	n	%	n	%	n	%
Age						
18 to 24	236	41.1	167	47.7	84	33.3
25 to 29	109	19.0	53	15.1	61	24.2
30 to 34	81	14.1	51	14.6	32	12.7
35 to 40	148	25.8	79	22.6	75	29.8
Race						
Caucasian/White	302	52.6	243	69.4	71	28.2
African American/Black	188	32.8	62	17.7	135	53.6
Native American	1	0.2	1	0.3	1	0.4
Asian	10	1.7	7	2.0	4	1.6
Other	73	12.7	37	10.6	41	16.3
Education						
Less than High School	123	21.4	25	7.1	104	41.3
Completed High School	214	37.3	126	36.0	100	39.7
Some College/Technical School	167	29.1	131	37.4	44	17.5
Graduated College / Technical School or more	70	12.2	68	19.4	4	1.6
Income						
\$0 to \$14,999	169	29.4	45	12.9	129	51.2
\$15,000 to \$24,999	126	22.0	65	18.6	69	27.4
\$25,000 to \$34,999	75	13.1	55	15.7	27	10.7
\$35,000 to \$44,999	61	10.6	48	13.7	14	5.6
\$45,000 to \$64,999	57	9.9	55	15.7	7	2.8
\$65,000 to \$74,999	29	5.1	27	7.7	2	0.8
\$75,000 or more	53	9.2	52	14.9	3	1.2
Refused	4	0.7	3	0.9	1	0.4

†Includes low literacy respondents from the General Population (n=28) as well as the additional enriched low literacy completes (n=224)
Source: Table 5 of Study 92062 Report.

The primary objective of this study was to evaluate the subject's ability to understand the enhanced pregnancy warning, (b) (4)

Demonstrated comprehension was determined based on the combination of the closed-end and open-end questions.

The comprehension results for this primary communication objective appear in the following table and are presented for both the GP cohort and LL respondents. General Population comprehension scores were 92.9% (n=325, LCI=89.6%). Low Literacy respondents' scores were somewhat lower at 83.3% (n=210, LCI=78.1%).

Table 18: Study 92062 Analysis of Enhanced Pregnancy Warning

Total Responding	GP Females of Childbearing Age (N=350)		NL Females of Childbearing Age ¹ (N=322)		† LL Females of Childbearing Age (N=252)	
	n	% (95% CI ²)	n	% (95% CI ²)	n	% (95% CI ²)
<u>Demonstrate Comprehension</u>	325	92.9% (89.6%, 95.3%)	300	93.2% (89.8%, 95.7%)	210	83.3% (78.1%, 87.7%)

Abbreviation: NL = Normal Literacy, LL = Low Literacy
 †Includes low literacy respondents from the General Population (n=28) as well as the additional enriched low literacy completes (n=224).
¹ Normal literacy estimates were calculated by the statistical reviewer.
² CI is based on exact confidence limit.
 Source: Table 6 of Study 92062 Report. However, the upper bounds of the CI were calculated by the statistical reviewer since they were not included in the Applicant's submission.

4.3 Full Label Comprehension Study among 65+ Women (Protocol #92101)

This quantitative, full label comprehension study was designed to assess whether women over 65 were able to comprehend the Oxytrol label, including uses, warnings, and directions, which are illustrated on the packaging as Drug Facts.

This study was designed to evaluate the consumer's ability to comprehend the Oxytrol label including uses, warnings, and directions, among a general population of women 65 years of age and older who self-reported OAB symptoms.

A single cohort of females was evaluated in this study representing the general population. The target population consisted of females suffering from OAB symptoms ages 65 years or older. This population was recruited using site databases.

The primary objective of this study was to measure respondent comprehension of the warnings on the outer carton for the following communication objectives:

1. Product Use:
 - a. Treats overactive bladder in women
 - b. You may be suffering from overactive bladder if you have had 2 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:
 - i. Have any of the following symptoms
 1. Pain or burning when urinating. These symptoms could be accompanied by a fever or chills.
 2. Blood in your urine
 3. Lower back or side pain
 4. Urine that is cloudy or foul-smelling
 - ii. Only experience accidental urine loss when you cough, sneeze or laugh, you may have stress incontinence. This product will not work for that condition.
 - iii. Have urinary retention (are not able to empty your bladder)
 - iv. Have been told by a doctor that you have gastric retention (your stomach empties slowly after a meal)
 - v. Narrow-angle glaucoma
 - vi. Are allergic to oxybutynin
- b. Ask a doctor before use if you have:
 - i. A history of diabetes in your immediate family
 - ii. Unexplained weight loss
 - iii. A history of kidney stones
 - iv. Liver or kidney disease
- c. Ask a doctor or pharmacist before use if you are:
 - i. Taking prescription medicine for overactive bladder
 - ii. Taking a diuretic (commonly called water pills)
- d. Stop Use and Ask a Doctor if:
 - i. Condition worsens, or if new symptoms appear
 - ii. Condition does not improve after 2 weeks of use
 - iii. You have an allergic reaction to this product
 - iv. You have severe redness, itchiness or blistering at the site of application
- e. How to use the patch
 - i. Wear only 1 patch at a time for 4 days in a row
 - ii. After 4 days, remove the used patch and apply a new one

The primary endpoint for this study was the number of general population subjects who had a correct overall response for the primary communication objective. The primary analysis consisted of estimating the correct comprehension rate for the general population. The rate was computed as the number of subjects with an overall correct response divided by the number of subjects in the general population who answered the question. The lower bound of two-sided 95% confidence limit was computed using the exact method. If the lower confidence limit was at least 90%, it was concluded that the objective was comprehended.

A sample of 350 respondents in the general population cohort provides 92% power to conclude that the true comprehension rate for the primary objective is at least 90% when the observed comprehension rate is 95% or higher, based on a two-sided exact test at the 5% level.

All three hundred fifty (350) respondents completed the study. For the total study population (n=350), age ranges were comprised of an older population, by study design, and consisted of those who suffer from OAB symptoms. A more specific age breakdown is illustrated in the following table, with the largest age group represented being 65-69 years of age (n=186, 53.1%). For this general population single cohort, the majority of respondents were Caucasian (n=310, 88.6 %). Furthermore the largest represented educational level was noted to be “Completed High School” (n=138, 39.4%) and income ranges were evenly dispersed.

Table 19: Study 92101 Responders’ Gender, Age, Race, Ethnicity, Education, and Income

	Total, GP Females with OAB, Age 65+ (N=350)		NL Females with OAB, Age 65+ (N=307)		LL Females with OAB, Age 65+ (N=43)	
	n	%	n	%	n	%
Age						
65 to 69	186	53.1	159	51.8	27	62.8
70 to 74	97	27.7	86	28.0	11	25.6
75 to 79	51	14.6	47	15.3	4	9.3
80 or above	16	4.6	15	4.9	1	2.3
Race						
Caucasian/White	310	88.6	280	91.2	30	69.8
African American/Black	31	8.9	21	6.8	10	23.3
Native American	1	0.3	1	0.3	--	--
Asian	1	0.3	--	--	1	2.3
Other	7	2.0	5	1.6	2	4.7
Education						
Less than High School	15	4.3	10	3.3	5	11.6
Completed High School	138	39.4	118	38.4	20	46.5
Some College/Technical School	122	34.9	108	35.2	14	32.6
Graduated College / Technical School or more	75	21.4	71	23.1	4	9.3
Income						
\$0 to \$14,999	35	10.0	29	9.4	6	14.0
\$15,000 to \$24,999	62	17.7	53	17.3	9	20.9
\$25,000 to \$34,999	87	24.9	73	23.8	14	32.6
\$35,000 to \$44,999	54	15.4	51	16.6	3	7.0
\$45,000 to \$64,999	56	16.0	48	15.6	8	18.6
\$65,000 to \$74,999	14	4.0	14	4.6	--	--

	Total, GP Females with OAB, Age 65+ (N=350)		NL Females with OAB, Age 65+ (N=307)		LL Females with OAB, Age 65+ (N=43)	
	n	%	n	%	n	%
Income \$75,000 or more	21	6.0	19	6.2	2	4.7
Refused	21	6.0	20	6.5	1	2.3

(--) Indicates a percentage that does not round to 1 or is zero.
Source: Table 6 of Study 92101 Report.

As shown in the table below, 7 of the 26 primary communication objectives met the threshold. All primary objectives related to the “Directions” met or exceeded the lower bound threshold. In addition, one "Stop use and ask a doctor" and two "Do not use" symptoms exceeded the lower bound threshold.

Table 20: Study 92101 Analysis of Primary Communication Objectives – Met Threshold

Total Responding	Total N=350	
	n	% (95% CI ¹)
One Patch Worn at a Time (Q21) <u>Demonstrate Comprehension</u>	347	99.1% (97.5%, 99.8%)
Product Use (Q1) <u>Demonstrate Comprehension</u>	346	98.9% (97.1%, 99.7%)
Wear Second Patch for 4 Days (Q6) <u>Demonstrate Comprehension</u>	342	97.7% (95.5%, 99.0%)
Stop Use and Ask a Doctor, Symptoms Getting Worse (Q24) <u>Demonstrate Comprehension</u>	342	97.7% (95.5%, 99.0%)
Wear First Patch for 4 Days <u>Demonstrate Comprehension</u>	341	97.4% (95.2%, 99.8%)
Not Okay, Blood in Urine (Q16) <u>Demonstrate Comprehension</u>	337	96.3% (93.7%, 98.0%)
Not Okay, Pain while Urinating (Q23) <u>Demonstrate Comprehension</u>	334	95.4% (92.7%, 97.4%)

¹ CI is based on exact confidence limit.
Source: Table 7 of Study 92101 Report. However, the upper bounds of the CI were calculated by the statistical reviewer since they were not included in the Applicant's submission.

As shown in the following table, a number of primary communication objectives (8 of 26) were within 5 percentage points of the 90% lower bound threshold. These were in most of the response categories: “Ask a doctor,” “Ask a doctor or pharmacist,” "Do not use," and “Stop use and ask a doctor” sections of the DFL.

Table 21: Study 92101 Analysis of Primary Communication Objectives – Within 5 Percentage Points of Threshold

Total Responding	Total N=350	
	n	% (95% CI ¹)
Not Okay, Pain in Lower Back (Q19) <u>Demonstrate Comprehension</u>	322	92.0% (88.6%, 94.6%)
Ask a Doctor, Family History of Diabetes (Q25) <u>Demonstrate Comprehension</u>	321	91.7% (88.3%, 94.4%)
Not Okay, Foul-Smelling Urine (Q2) <u>Demonstrate Comprehension</u>	321	91.7% (88.3%, 94.4%)
Ask a Doctor/Pharmacist, Current Rx User (Q4) <u>Demonstrate Comprehension</u>	320	91.4% (88.0%, 94.1%)
Stop Use and Ask a Doctor, Conditions Has Not Improved (Q8) <u>Demonstrate Comprehension</u>	317	90.6% (87.0%, 93.4%)
Ask a Doctor, Losing Weight for No Reason (Q12) <u>Demonstrate Comprehension</u>	316	90.3% (86.7%, 93.2%)
Not Okay, Allergic to Oxybutynin (Q7) <u>Demonstrate Comprehension</u>	315	90.0% (86.4%, 92.9%)
Stop Use and Ask a Doctor, Allergic Reaction (Q20) <u>Demonstrate Comprehension</u>	312	89.1% (85.4%, 92.2%)

¹ CI is based on exact confidence limit.
Source: Table 8 of Study 92101 Report. However, the upper bounds of the CI were calculated by the statistical reviewer since they were not included in the Applicant's submission.

The following table shows the communication objectives that did not meet the threshold.

Table 22: Study 92101 Analysis of Primary Communication Objectives – Greater than 5 Percentage Points from Threshold

Total Responding	Total N=350	
	n	% (95% CI ¹)
Not Okay, Has Urinary Retention (Q30) <u>Demonstrate Comprehension</u>	303	86.6% (82.5%, 90.0%)
Ask a Doctor, Kidney Stone (Q15) <u>Demonstrate Comprehension</u>	302	86.3% (82.2%, 89.7%)
Not Okay, Has Narrow-Angle Glaucoma (Q10) <u>Demonstrate Comprehension</u>	299	85.4% (81.3%, 90.0%)
Stop Use and Ask a Doctor, Developed Blisters and Red and Itchy (Q13) <u>Demonstrate Comprehension</u>	298	85.1% (81.0%, 88.7%)
Not Okay, Gastric Retention (Q14) <u>Demonstrate Comprehension</u>	297	84.9% (80.7%, 88.5%)
Ask a Doctor, Has Liver Disease (Q27) <u>Demonstrate Comprehension</u>	296	84.6% (80.4%, 88.2%)
Continue Using Product, Condition Has Improved a Lot (Q18) <u>Demonstrate Comprehension</u>	292	83.4% (79.1%, 87.2%)
Ask a Doctor/Pharmacist, Taking Water Pills (Q22) <u>Demonstrate Comprehension</u>	288	82.3% (77.9%, 86.1%)
Have Symptoms of OAB for at Least 3 Months (Q11) <u>Demonstrate Comprehension</u>	275	78.6% (73.9%, 82.8%)
Okay, Urinate More Often and Leaking Accidents (Q3) <u>Demonstrate Comprehension</u>	255	72.9% (67.9%, 77.5%)
Not Okay, Accidentally Urinates When Sneezes (Q9) <u>Demonstrate Comprehension</u>	250	71.4% (66.4%, 76.1%)

¹ CI is based on exact confidence limit.
Source: Table 9 of Study 92101 Report. However, the upper bounds of the CI were calculated by the statistical reviewer since they were not included in the Applicant's submission.

The following tables show differences in scores based on Literacy levels. In most cases, the scores of low literate respondents were within five percentage points of normal literate respondents. In just three cases were the scores more than 10 points apart: allergic to oxybutynin, urinary retention, and stress incontinence (accidentally urinates when sneezes).

Table 23: Study 92101 Analysis of Primary Communication Objectives by Literacy-Met or Exceeded Threshold within Normal Literacy Subgroup

Total Responding	Normal Literacy 307			Low Literacy 43		
	n	%	* Lower Bound	n	%	* Lower Bound
Card U: One patch worn at a time (Q21)	305	99.3	97.7	42	97.7	87.7
Card A: Product use (Q1)	304	99.0	97.2	42	97.7	87.7
Card F: Wear second patch for 4 days (Q6)	302	98.4	96.2	40	93.0	80.9
Card X: Stop use and ask a doctor, symptoms getting worse (Q24)	299	97.4	94.9	43	100.0	91.8
Card E: Wear first patch for 4 days (Q5)	301	98.0	95.8	40	93.0	80.9
Card P: Not okay, blood in urine (Q16)	298	97.1	94.5	39	90.7	77.9
Card W: Not okay, pain while urinating (Q23)	295	96.1	93.3	39	90.7	77.9

Source: Table 20 of Study 92101 Report.

Table 24: Study 92101 Analysis of Primary Communication Objectives by Literacy – Within 5 Percentage Points of Threshold within Normal Literacy Subgroup

Total Responding	Normal Literacy 307			Low Literacy 43		
	n	%	* Lower Bound	n	%	* Lower Bound
Card S: Not okay, pain in lower back (Q19)	285	92.8	89.4	37	86.0	72.1
Card Y: Ask a doctor, family history of diabetes (Q25)	283	92.2	88.6	38	88.4	74.9
Card B: Not okay, foul-smelling urine (Q2)	283	92.2	88.6	38	88.4	74.9
Card D: Ask a doctor/pharmacist, current Rx user (Q4)	284	92.5	89.0	36	83.7	69.3
Card H: Stop use and ask a doctor, conditions has not improved (Q8)	279	90.9	87.1	38	88.4	74.9
Card L: Ask a doctor, losing weight for no reason (Q12)	278	90.6	86.7	38	88.4	74.9
Card G: Not okay, allergic to oxybutynin (Q7)	281	91.5	87.8	34	79.1	64.0
Card T: Stop use and ask a doctor, allergic reaction (Q20)	273	88.9	84.9	39	90.7	77.9

Source: Table 21 of Study 92101 Report.

Table 25: Study 92101 Analysis of Primary Communication Objectives by Literacy – Did Not Meet Threshold within Normal Literacy Subgroup

Total Responding	Normal Literacy 307			Low Literacy 43		
	n	%	* Lower Bound	n	%	* Lower Bound
Card DD: Not okay, has urinary retention (Q30)	270	87.9	83.8	33	76.7	61.4
Card O: Ask a doctor, kidney stones (Q15)	267	87.0	82.7	35	81.4	66.6
Card J: Not okay, has narrow-angle glaucoma (Q10)	265	86.3	82.0	34	79.1	64.0
Card M: Stop use and ask a doctor, developed blisters and red and itchy (Q13)	262	85.3	80.9	36	83.7	69.3
Card N: Not okay, gastric retention (Q14)	264	86.0	81.6	33	76.7	61.4
Card AA: Ask a doctor, has liver disease (Q27)	261	85.0	80.5	35	81.4	66.6
Card R: Continue using product, condition has improved a lot (Q18)	257	83.7	79.1	35	81.4	66.6
Card V: Ask a doctor/pharmacist, taking water pills (Q22)	254	82.7	78.0	34	79.1	64.0
Card K: Have symptoms of OAB for at least 3 months (Q11)	245	79.8	74.9	30	69.8	53.9
Card C: Okay, urinate more often and leaking accidents (Q3)	221	72.0	66.6	34	79.1	64.0
Card I: Not okay, accidentally urinates when sneezes (Q9)	232	75.6	70.4	18	41.9	27.0

Source: Table 22 of Study 92101 Report.

The results of this label comprehension study show varying degrees of success in communication of the key messages. The general population met or exceeded (92.7% - 97.5%) the lower bound threshold of 90% on 7 of 26 of the primary communication objectives. A number of the other primary objectives (8 of 26) missed it by 5 percentage points or less.

4.4 Initial 2008 Label Comprehension Study (Protocol #82023)

This is a multi-site, single-visit, label comprehension study was conducted from May 29 – June 11, 2008. A total of 675 subjects were recruited from 16 market research centers well distributed throughout the United States. Four (4) cohorts were recruited and interviewed consisting of normal literate (NL) female sufferers of overactive bladder (OAB - Cohort 1), low literate (LL) female sufferers of OAB (Cohort 2), general sample of female non-sufferers of OAB (Cohort 3) and general sample of males (Cohort 4).

The objectives of the study were, for Cohorts 1, 2, and 3 to evaluate subject comprehension of key safety and risk communication objectives for product use, directions for use, and product warnings found on the Drug Facts Label (DFL) for OTC Oxybutynin Transdermal System. For Cohort 4, the objective was to evaluate whether men understood that this product is for women only. In order to achieve these study objectives, subject comprehension of a total of 30 primary communication objectives and three (3) secondary communication objectives were tested.

The purpose of this study was to determine if appropriate subject comprehension of key communication objectives found on the product DFL have been met. The primary statistical analysis consisted of computing point estimates and lower 97.5% confidence bounds for the

proportion of subjects who successfully met each communication objective (“demonstrated comprehension”). Point estimates for each question were reported for all four (4) cohorts. The study’s success criteria for the primary and secondary communication objectives are detailed below.

Additional analyses were performed to determine if there were significant differences in point estimates of comprehension by cohort. The relevant proportions were statistically tested against one another using a z-test. In this study, a difference was considered statistically significant if it had a p-value of ≤ 0.05 .

The “primary” communication objectives identified on the drug fact labeling (DFL) are labeling messages related to product use, warnings and directions. The ONP has recommended that the threshold for these objectives be set at 90%.

Although 30 of the 33 communication objectives tested in this study were defined as “primary” by the ONP, consideration should be given to the fact that within this category, there are levels of medical risk associated with misunderstanding a particular label communication. Within this category the objectives range from those that present a significant medical risk to consumers (i.e., do not use if have pain when urinating, stop use and ask a doctor if condition worsens, etc.) and others that present a minimal risk (i.e., do not use to treat symptoms of stress incontinence).

The following table lists the study subjects’ demographics.

Table 26: Study 82023 Disposition of Subjects - Gender, Age, Race, Ethnicity, Education, and Income

	NL Female Sufferers with OAB (C1)		LL Female Sufferers with OAB (C2)		GS of Female Non-Sufferers (C3)		GS of Males (C4)	
Total Responding	196		204		199		76	
	n	%	n	n	%	%	n	%
Age								
18 to 24	12	6.1	12	5.9	19	9.5	31	40.8
25 to 34	20	10.2	29	14.2	26	13.1	19	25.0
35 to 44	31	15.8	40	19.6	44	22.1	9	11.8
45 to 54	58	29.6	58	28.4	45	22.6	9	11.8
55 to 64	35	17.9	43	21.1	37	18.6	4	5.3
65 to 74	32	16.3	18	8.8	22	11.1	2	2.6
75 or older	8	4.1	4	2.0	6	3.0	2	2.6
Race								
Caucasian/White	170	86.7	125	61.3	156	78.4	54	71.1
African American/Black	23	11.7	58	28.4	34	17.1	6	7.9
Native American	1	0.5	1	0.5	--	--	--	--
Asian	--	--	4	2.0	--	--	--	--
Other	2	1.0	16	7.8	9	4.5	16	21.1
Education								
Less than High School	7	3.6	28	13.7	9	4.5	8	10.5
Completed High School	57	29.1	115	56.4	54	27.1	41	53.9
Some College/Technical School	71	36.2	57	27.9	90	45.2	20	26.3

	NL Female Sufferers with OAB (C1)		LL Female Sufferers with OAB (C2)		GS of Female Non-Sufferers (C3)		GS of Males (C4)	
Total Responding	196		204		199		76	
	n	%	n	n	%	%	n	%
Education Graduated College / Technical School or more	61	31.1	4	2.0	46	23.1	7	9.2
Income								
\$0 to \$14,999	20	10.2	36	17.6	20	10.1	19	25.0
\$15,000 to \$24,999	31	15.8	55	27.0	22	11.1	18	23.7
\$25,000 to \$34,999	27	13.8	59	28.9	39	19.6	17	22.4
\$35,000 to \$44,999	32	16.3	23	11.3	26	13.1	9	11.8
\$45,000 to \$64,999	35	17.9	12	5.9	31	15.6	8	10.5
\$65,000 to \$74,999	15	7.7	8	3.9	20	10.1	1	1.3
\$75,000 or more	30	15.3	10	4.9	33	16.6	1	1.3
Refused	6	3.1	1	0.5	8	4.0	3	3.9

Source: Table 8 of Study 92101 Report.

Overall, the results demonstrated that subjects understood this product label quite well. Subjects demonstrated excellent comprehension of the product’s use for treatment of OAB (96-100%) and also showed strong understanding of OAB symptoms (83-91%). All cohorts showed understanding that this product is not for use by males (87-95%) or those under 18 years of age (99-100%).

All of the primary communication objectives related to “Directions for use” were well understood by subjects (96-100%). Subjects understood when and how often to apply a new patch and also demonstrated an understanding of how to properly dispose of the patch and what to do if one (1) patch is accidentally ingested.

A communication objective testing comprehension of what to do if there is blood in the urine, was tested as a possible indicator of bladder cancer. The scores for this high risk objective were excellent (94-95%) and showed that subjects understood this message well. Subjects also demonstrated strong comprehension of objectives regarding possible urinary tract infection (UTI) or kidney infection symptoms, specifically strange colored urine (84-92%), lower back pain (91-95%), and pain when urinating (91-97%).

Four (4) communication objectives were tested from the “Stop use and ask a doctor” section of the DFL. The scores at two (2) of the objectives (condition is getting worse and having an allergic reaction), were strong, 88-90% and 90-97% respectively, while the remaining two (2) objectives (condition not improved and skin blistering and very red) yielded lower scores, 69-77% and 79-83% respectively. When evaluating the expectation that subjects will give a precise two-part response, the scores appear lower; however, when considering the general gestalt of the correct response to discontinue use and/or consult a medical professional, it is clear that subjects understood all four (4) of these important safety messages (93-95%).

The lower scores for the “Stop use and ask a doctor” area of the label are due in large part to the fact that subjects must verbalize both “stop use” and “ask a doctor” in order to be considered

“correct”. These objectives are subjected to a particularly conservative coding approach that centers on the idea that when subjects respond to a question by saying that they would “ask a doctor” it indicates, by default, that they did not understand the objective. However, it can be argued that if any part of an “ask a doctor” message appears within the area of the label in question (i.e., Stop use and ask a doctor area of the DFL), then an “ask a doctor” response should be considered “correct”. For communication objectives that appear in the “Stop use and ask a doctor” section of the DFL, this point of view is supported in the following two (2) ways:

1. In addition to discontinuing use of the product, the label also recommends that a doctor be consulted, which suggests that coding this response “incorrect” is overly stringent.
2. Upon further analysis of the responses given at the “Stop use and ask a doctor” questions, there is no evidence to support the conclusion that subjects are simply defaulting to “asking a doctor” and do not understand the objectives. If this were the case, it would be expected that across these objectives, a consistent proportion of subjects would give that response. Judging by the fact that this proportion changes (e.g., Cohort 1 went from Card H =22%, Card O=9%, Card V=8%, and finally Card Y=10%), it appears that in some instances subjects determined that their primary response would be to “ask a doctor”, while in others it would be to “stop use”.

5 Self-Selection Studies

For all the label comprehension and self-selection studies’ results, the Applicant only provided the lower bound of the 95% CI without the upper bound; the statistical reviewer calculated and presented the most of the 95% CI with both upper bound and lower bound.

5.1 Targeted Self-Selection Study in Pregnant Women (Protocol #10054)

This quantitative self-selection study was designed to assess whether pregnant women were able to make a correct self-selection decision about Oxytrol based on the warning that if pregnant, they should not choose to use the product and/or a healthcare professional should be consulted prior to use. The proposed labeling for Oxytrol includes explicit text to communicate this advice:

-  (b) (4)
- “If pregnant or breastfeeding, ask a health professional before use.”

This study was designed to evaluate consumers’ ability to make a correct self-selection decision based on the product labeling.

Two (2) cohorts were evaluated in this study: a general population of pregnant women, ages 18 to 40, who self-report they suffer from urinary symptoms (Cohort 1) and an enriched sample of low literate pregnant woman, ages 18 to 40, who self-report they suffer from urinary symptoms (Cohort 2).

A total of 435 respondents were recruited and interviewed at nine (9) market research facilities geographically dispersed throughout the United States. All four hundred thirty-five (435)

respondents completed the study. The demographics and other characteristics of the respondents completing this self-selection study are included below in the following table.

Table 27: Study 10054 Responders' Gender, Age, Race, Ethnicity, Education, and Income

	Total (N=435)		GP Pregnant Females with Urinary Symptoms (N=308)		† LL Pregnant Females with Urinary Symptoms (N=142)	
	n	%	n	%	n	%
Age						
18 to 24	120	27.6	57	18.5	71	50.0
25 to 29	135	31.0	102	33.1	39	27.5
30 to 34	111	25.5	96	31.2	16	11.3
35 to 40	69	15.9	53	17.2	16	11.3
Pregnancy						
3 months or less	186	42.8	103	33.4	87	61.3
4 to 6 months	129	29.7	104	33.8	30	21.1
7 to 9 months	120	27.6	101	32.8	25	17.6
Race						
Caucasian/White	226	52.0	221	71.8	11	7.7
African American/Black	168	38.6	63	20.5	111	78.2
Native American	6	1.4	5	1.6	1	0.7
Asian	5	1.1	4	1.3	2	1.4
Other	30	6.9	15	4.9	17	12.0
Education						
Less than High School	80	18.4	15	4.9	69	48.6
Completed High School	110	25.3	57	18.5	58	40.8
Some College/Technical School	100	23.0	92	29.9	13	9.2
Graduated College / Technical School or more	145	33.3	144	46.8	2	1.4
Income						
\$0 to \$14,999	144	33.1	39	12.7	111	78.2
\$15,000 to \$24,999	56	12.9	42	13.6	18	12.7
\$25,000 to \$34,999	34	7.8	31	10.1	4	2.8
\$35,000 to \$44,999	35	8.0	33	10.7	2	1.4
\$45,000 to \$64,999	63	14.5	60	19.5	6	4.2
\$65,000 to \$74,999	27	6.2	27	8.8	--	--
\$75,000 or more	72	16.6	72	23.4	1	0.7
Refused	4	0.9	4	1.3	--	--
†Includes low literacy respondents from the General Population (n=15) as well as the additional enriched low literacy completes (n=127) Source: Table 5 of Study 10054 Report.						

The primary endpoint for this study was the number of respondents who provided a correct overall response for the self-selection question. The rate was computed by the number of general population respondents with an overall correct response divided by the number of respondents who answered the question. Two-sided 95% confidence limits were computed using the exact

method. If the lower confidence limit was at least 90%, it was concluded that the self-selection objective had been met.

A sample of 350 respondents in the general population cohort provides a 92% power to conclude that the true self-selection rate for the primary objective is at least 90% when the observed self-selection rate is 95% or higher based on a two-sided exact test at the 5% level.

The pre-mitigation and post-mitigation self-selection results appear in the following table and are presented for the general population cohort, the normal literate women, and low literacy cohort. Seventeen responses were considered for mitigation for various reasons (i.e., subject mentioned a doctor at the third probe, subject appeared to be responding to initial question as if she weren't currently pregnant, subject answered the question as though it were a hypothetical situation, subject's response never provided incorrect information). When these responses are mitigated to be considered a correct response, 91.6% (LCI= 87.5%) of the general population and 67.6% of the low literacy respondents made a correct self-selection decision.

Table 28: Study 10054 Analysis of Self-Selection Pre- and Post-Mitigation

Total Responding	GP Pregnant Females with Urinary Symptoms (N=308)		NL Pregnant Females with Urinary Symptoms ¹ (N=293)		† LL Pregnant Females with Urinary Symptoms (N=142)	
	n	% (95% CI ²)	n	% (95% CI ²)	n	% (95% CI ²)
Pre-Mitigation						
<u>Correct Self-Selection</u>	272	88.3% (84.2%, 91.7%)	261	89.1% (84.9%, 92.4%)	89	62.7% (54.2%, 70.6%)
Post-Mitigation						
<u>Correct Self-Selection</u>	282	91.6% (87.9%, 94.4%)	271	92.5% (88.9%, 95.2%)	96	67.6% (59.2%, 75.2%)

Abbreviation: NL = Normal Literacy, LL = Low Literacy
 †Includes low literacy respondents from the General Population (n=15) as well as the additional enriched low literacy completes (n=127)
¹ Normal literacy estimates were calculated by the statistical reviewer.
² CI is based on exact confidence limit.
 Source: Table 6 and 16 of Study 10054 Report. However, the upper bounds of the CI were calculated by the statistical reviewer since they were not included in the Applicant's submission.

5.2 Targeted Self-Selection Study in Men (Protocol #92061)

This quantitative self-selection study was designed to assess whether men are able to make the correct decision about selecting the product given a label that states it is intended for use by women only. The proposed labeling for Oxytrol includes explicit text and visual cues to indicate that it is for women.

- The proposed package prominently states “for women” on the PDP.
- The Drug Facts indicate that the product should be used to treat overactive bladder in women and states do not use if you are male.
- The directions state for women 18 years and older.
- The colors, pink and yellow, are traditionally more feminine colors.

- There is a female stick figure featured prominently on the front panel, actually leaning on the "O" of Oxytrol.

Two (2) cohorts were evaluated in this study. The target population consisted of males, ages 18 and older, who self-reported that they suffered from urinary symptoms. This population was recruited using site databases. The data from this study will be used to determine the need for further labeling adjustments.

The primary objective of this study was to measure self-selection after reviewing the Oxytrol OTC package label in a general population of men who self-report OAB symptoms. Specifically, men should have chosen not to select the product based on the "Do not use if you are male" warning on the label.

The primary endpoint for this study was the number of respondents who had a correct overall response for the self-selection question. The rate was computed as the number of general population respondents with an overall correct response divided by the number of respondents who answered the question. Two-sided 95% confidence limits were computed using the exact method. If the lower confidence limit was at least 90%, it was concluded that the self-selection objective had been met.

A sample of 350 respondents in the general population cohort provides 92% power to conclude that the true self-selection rate for the primary objective is at least 90% when the observed self-selection rate is 95% or higher, based on a two-sided exact test at the 5% level. A sample size of 250 respondents in the total low literacy cohort provides 80% power to conclude that the true self-selection rate for the primary objective is at least 90% when the observed self-selection rate is 95% or higher, based on a two-sided exact test at the 5% level.

A total of 571 respondents were recruited and interviewed at nine (9) market research facilities geographically dispersed throughout the United States. All five hundred seventy-one (571) respondents completed the study. For the total study population, age ranges were fairly even across the ages of 18 to 69. Ages ranged from (18-29: n=165, 28.9%; 30-40: n=125, 21.9%; 41-49: n=104, 18.2%; 50-59: n=92, 16.1%; 60 and older: n=85, 14.9%). For the GP cohort, the majority of respondents were Caucasian (n=312, 54.6 %) followed by African-American (n=204, 35.7%) and other (n=55, 9.6%). A total of 5.8% (n=33) of respondents were Hispanic. Most respondents had completed a high school education (n=236, 41.3%) and income ranges varied across respondents. The demographics and other characteristics of the respondents completing this study are included below.

Table 29: Study 92061 Responders' Gender, Age, Race, Ethnicity, Education, and Income

	Total (N=571)		GP Males with Urinary Symptoms (N=354)		† LL Males with Urinary Symptoms (N=273)	
	n	%	n	%	n	%
Age						
18 to 29	165	28.9	105	29.6	79	28.9
30 to 40	125	21.9	75	21.2	64	23.4
41 to 49	104	18.2	47	13.3	65	23.8
50 to 59	92	16.1	54	15.2	44	16.1
60 or older	85	14.9	73	20.6	21	7.7
Race						
Caucasian/White	312	54.6	257	72.6	84	30.8
African American/Black	204	35.7	63	17.8	161	59.0
Native American	2	0.4	2	0.6	--	--
Asian	9	1.6	7	2.0	3	1.1
Other	44	7.7	25	7.1	25	9.2
Education						
Less than High School	117	20.5	16	4.5	106	38.8
Completed High School	236	41.3	148	41.8	120	93.8
Some College/Technical School	140	24.5	112	31.6	42	15.4
Graduated College / Technical School or more	78	13.7	78	22.0	5	1.8
Income						
\$0 to \$14,999	197	34.5	43	12.1	166	60.8
\$15,000 to \$24,999	100	17.5	60	16.9	52	19.0
\$25,000 to \$34,999	66	11.6	52	14.7	27	9.9
\$35,000 to \$44,999	56	9.8	48	13.6	12	4.4
\$45,000 to \$64,999	66	11.6	65	18.4	9	3.3
\$65,000 to \$74,999	29	5.1	29	8.2	4	1.5
\$75,000 or more	53	9.3	53	15.0	2	0.7
Refused	4	0.7	4	1.1	1	0.4

†Includes low literacy respondents from the General Population (n=56) as well as the additional enriched low literacy completes (n=217).
Source: Table 5 of Study 92061 Report.

The self-selection results appear in the following table and are presented for the GP cohort, normal literate, and low literate respondents. General Population self-selection scores were 90.1% (n=319, LCI=86.5%) and Low Literacy respondents had identical self-selection results with 90.1% (n=246, LCI=85.9%). Responses were coded as correct if the respondent answered “no” to the self-selection decision and/or if the follow-up questions demonstrated that the respondent understood that the product was not for use by men.

Table 30: Study 92061 Analysis of Self-Selection Pre- and Post-Mitigation

Total Responding	GP Males with Urinary Symptoms (N=354)		NL Males with Urinary Symptoms ¹ (N=298)		† LL Males with Urinary Symptoms (N=273)	
	n	% (95% CI ²)	n	% (95% CI ²)	n	% (95% CI ²)
Pre-Mitigation						
<u>Correct Self-Selection</u>	319	90.1% (86.5%, 93.0%)	319	91.3% (87.5%, 94.2%)	246	90.4% (86.3%, 93.7%)

Abbreviation: NL = Normal Literacy, LL = Low Literacy
† Includes low literacy respondents from the General Population (n=56) as well as the additional enriched low literacy completes (n=217).
¹ Normal literacy estimates were calculated by the statistical reviewer.
² CI is based on exact confidence limit.
Source: Table 6 and 10 of Study 92061 Report. However, the upper bounds of the CI were calculated by the statistical reviewer since they were not included in the Applicant's submission.

5.3 Initial Self-Selection Study (Protocol #CL2008-19)

This study was designed to provide diagnostic information about the consumer's ability to correctly self-diagnose whether they did or did not have overactive bladder and also to evaluate the consumer's ability to make a correct self-selection decision based on their personal medical history and the product labeling.

Three (3) Cohorts were evaluated in this study. The target population (Cohorts 1 and 2) consisted of females, ages 18 and older, who self-reported that they suffered from urinary symptoms. This population was recruited using mass advertising such as newspaper, radio and community outreach.

Cohort 3 consisted of subjects who suffered from urinary symptoms, but also had a condition that advises the consumer to ask a doctor before use (such as diabetes, glaucoma, or pregnancy/nursing) or who should not use the product (males).

Table 31: Study CL2008-19 Cohort Descriptions

Cohort	Description	Estimated Sample Size	Actual Sample Size
Cohort 1	Normal literate: Sufferers of urinary symptoms	N=216	N=218
Cohort 2	Low literate: Sufferers of urinary symptoms	N=216	N=137
Cohort 3	Contraindicated conditions: <ul style="list-style-type: none"> • Male • Diabetes • Glaucoma • Pregnant/Nursing 	N=216 (no less than n=10 in any one sub-population)	N=232 N=172 N=42 N=12 N=10

Source: Table 2 of Study CL2008-19 Report.

The primary variables for this study were:

- To evaluate consumers' ability to make a correct self-selection decision.
- To evaluate consumers' ability to correctly self-diagnose whether they do or do not have overactive bladder.

Self-Selection – Subjects were asked a selection question. (“Do you believe this product is appropriate for you to treat your symptoms of frequent urination, strong need to urinate right

away or inability to control the urge to urinate?’’) The 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. All other responses were considered incorrect and the reasons for those responses were obtained and analyzed.

Self-Diagnosis – Subjects were asked if they had symptoms of overactive bladder (OAB). (“Do you believe you have symptoms of overactive bladder, also known as OAB?’’) The responses to the diagnosis question were compared to the physician diagnosis. Correct diagnosis occurred if the response to the diagnosis question matched the physician diagnosis. Instances in which the diagnosis response did not match the physician response were considered incorrect.

Sample sizes were determined according to the following table.

Table 32: Study CL2008-19 Determination of Sample Size

Sample Size and Precision Reference Table at 95% Confidence Level Cohort	Precision Level (to lower bound) if Score is		
	80%	85%	90%
Cohort 1: Normal Literacy, Female Sufferers, Ages 18+	5% n=216	5% n=181	5% n=142
Cohort 2: Low Literacy, Female Sufferers, Ages 18+	5% n=216	5% n=181	5% n=142
Cohort 1: Contraindicated Conditions, Sufferers of OAB Symptoms, Ages 18+	5% n=216	5% n=181	5% n=142
<i>Based on 95% one-sided exact confidence interval</i>			
Source: Table 5 of Study CL2008-19 Report.			

The disposition of enrolled subjects in each Cohort is included in the tabulated study data reflected in the following table.

Table 33: Study CL2008-19 Subjects Disposition

	Cohort 1	Cohort 2	Cohort 1+2	Cohort 3
	N=246	N=152	N=398	N=234
Subject completed study ¹	218 (88.6%)	137 (90.1%)	355 (89.2%)	232 (99.1%)
Subject did not complete study	28 (11.4%)	15 (9.9%)	43 (10.8%)	2 (0.9%)
Primary Reason for not completing study				
Lost to follow-up	1 (3.6%)	0 (0.0%)	1 (2.3%)	0 (0.0%)
Subject withdrawal of consent	6 (21.4%)	5 (33.3%)	11 (25.6%)	0 (0.0%)
Other	21 (75.0%)	10 (66.7%)	31 (72.1%)	2 (100.0%)
¹ Cohorts 1 and 2: Subjects who review the package labeling, make a self-selection decision, sign the Informed Consent, make a self-diagnosis decision, participate in the medical evaluation of their symptoms and complete the final interview.				
Cohort 3: Subjects who review the package labeling and make a self-selection decision and complete the final interview.				
Source: Table 6 of Study CL2008-19 Report.				

The demographic characteristics of the study population are detailed in the following table.

Table 34: Study CL2008-19 Summary of Subject Demographic Characteristics (Subjects Who Completed Study)

	<u>Cohort 1</u> (N=218)	<u>Cohort 2</u> (N=137)	<u>Cohorts 1+2</u> (N=355)	<u>Cohort 3</u> (N=232)
Age (years)				
N	218	137	355	232
Mean	50.0	49.5	49.8	53.4
Standard Deviation (STD)	15.04	16.09	15.43	17.03
Median	49.0	50.0	49.0	54.0
Min-Max	18-86	18-93	18-93	18-91
18 to 35 years	37 (17.0%)	27 (19.7%)	64 (18.0%)	35 (15.1%)
36 to 55 years	109 (50.0%)	64 (46.7%)	173 (48.7%)	91 (39.2%)
56 to 70 years	51 (23.4%)	30 (21.9%)	81 (22.8%)	63 (27.2%)
>70 years	21 (9.6%)	16 (11.7%)	37 (10.4%)	43 (18.5%)
Gender				
Male				172 (74.1%)
Female	218 (100%)	137 (100%)	355 (100%)	60 (25.9%)
Race				
Caucasian	183 (83.9%)	103 (75.2%)	286 (80.6%)	169 (72.8%)
African American	31 (14.2%)	33 (24.1%)	64 (18.0%)	53 (22.8%)
Native American/Alaska Native	1 (0.5%)	0 (0.0%)	1 (0.3%)	1 (0.4%)
Asian/Pacific Islander	2 (0.9%)	0 (0.0%)	2 (0.6%)	6 (2.6%)
Other ^a	1 (0.5%)	1 (0.7%)	2 (0.6%)	3 (1.3%)
Ethnicity				
Hispanic or Latino	10 (4.6%)	21 (15.3%)	31 (8.7%)	14 (6.0%)
Not Hispanic or Latino	208 (95.4%)	116 (84.7%)	324 (91.3%)	218 (94.0%)
Education Level				
Some high school, high school degree or GED	60 (27.5%)	93 (67.9%)	153 (43.1%)	78 (33.8%)
Some college, technical school or college degree	150 (68.8%)	42 (30.7%)	192 (54.1%)	138 (59.7%)
Post Graduate Degree	8 (3.7%)	2 (1.5%)	10 (2.8%)	15 (6.5%)

^a Cohort 1 subject 6-20 had race of Hispanic, Cohort 2 subject 6-72 had race of Ecuadorian, Cohort 3 subject 2-39 had a race of Trinidad, 6-40 had a race of Spanish American, and 7-19 had a race of Patient did not clarify.

Note: Male subjects are eligible for Cohort 3 only.

Source: Table 10 of Study CL2008-19 Report.

Subjects in Cohorts 1 and 2 (normal and low literate sufferers of urinary symptoms) clearly demonstrated their ability to correctly self-diagnose the symptoms of overactive bladder. Of Cohorts 1 and 2, a total of 320/355 subjects self-diagnosed correctly (89.4% and 91.2%, respectively). These results highlight the ability of women to understand and distinguish the unique nature of these symptoms. By study design, those subjects in Cohort 3 did not undergo a medical history, medication history, laboratory testing, or physical examinations.

Table 35: Study CL2008-19 Analysis of self-diagnosis (subjects who completed study)

	<u>Cohort 1</u> (N=218)	<u>Cohort 2</u> (N=137)	<u>Cohorts 1+2</u> (N=355)	<u>Cohort 3</u> (N=232)
Correct self-diagnosis				
Yes	195 (89.4%)	125 (91.2%)	320 (90.1%)	
No	23 (10.6%)	12 (8.8%)	35 (9.9%)	
95% CI ^a for Yes	[85.4%, 100%]	[86.2%, 100%]	[87.1%, 100%]	
Correct self-diagnosis				
Correctly diagnosed overactive bladder	193 (99.0%)	125 (100%)	318 (99.4%)	
Correctly diagnosed no overactive bladder	2 (1.0%)	0 (0.0%)	2 (0.6%)	

^a95% one-sided exact confidence interval.

Note: By study design, Cohort 3 subjects do not make a self-diagnosis decision.

Source: Table 11 of Study CL2008-19 Report.

The self-selection data represent all three (3) Cohorts and indicate whether the subject made a correct or incorrect decision based on the package labeling and their unique and relevant medical history. The subject's decision was compared to the physician's selection decision.

Table 36: Study CL2008-19 Analysis of self-selection (subjects who completed study)

	<u>Cohort 1</u> (N=218)	<u>Cohort 2</u> (N=137)	<u>Cohorts 1+2</u> (N=355)	<u>Cohort 3</u> (N=232)
Correct self-selection				
Yes	178 (81.7%)	117 (85.4%)	295 (83.1%)	141 (60.8%)
No	40 (18.3%)	20 (14.6%)	60 (16.9%)	91 (39.2%)
95% CI ^a for Yes	[76.8%, 100%]	[79.5%, 100%]	[79.5%, 100%]	[55.2%, 100%]
Correct self-selection				
Correctly selected product	175 (98.3%)	117 (100%)	292 (99.0%)	2 (1.4%)
Correctly did not select product	3 (1.7%)	0 (0.0%)	3 (1.0%)	138 (97.9%)
Correctly wanted to ask a doctor first	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)

^a95% one-sided exact confidence interval.

Source: Table 13 of Study CL2008-19 Report.

Further detail for Cohort 3 is noted below. Cohort 3 was comprised of four (4) sub-populations, which included those who should not use the product (males) and those who should ask a doctor prior to use (those with diabetes, glaucoma, and those who are pregnant/nursing).

Table 37: Study CL2008-19 Analysis of self-selection by contraindication (Cohort 3 subjects who completed study)

	Male (N=172)	Diabetes (N=42)	Glaucoma (N=12)	Pregnant/Nursing (N=10)
Correct self-selection				
Yes	123 (71.5%)	11 (26.2%)	4 (33.3%)	4 (40.0%)
No	49 (28.5%)	31 (73.8%)	8 (66.7%)	6 (60.0%)
95% CI ^a for Yes	[65.3%, 100%]	[15.4%, 100%]	[12.3%, 100%]	[15.0%, 100%]
Correct self-selection				
Correctly did not select product	123 (100%)	8 (72.7%)	4 (100%)	4 (100%)
Correctly wanted to ask a doctor first	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)

^a 95% one-sided exact confidence interval.

Source: Table 14 of Study CL2008-19 Report.

6 EVALUATION OF SAFETY

The following table summarizes the AEs reported in the actual use study (CONTROL) for all subjects and by age cohort. A total of 975 AEs were reported by 519 of the 785 (66.1%) subjects treated with Oxytrol. Three hundred fifty-nine AEs (36.8% of the 975 AEs) were considered to be possibly or probably related to study product. AEs resulted in 141, and 38 subjects discontinuing use of study drug permanently or temporarily, respectively. AEs of 110 users who discontinued using study drug permanently and AEs of 21 users who temporarily discontinued using study drug were considered possibly or probably related to Oxytrol use.

Table 38: Study CL2008-13 (Actual Use Study) Clinical Adverse Experience Summary for the Actual Use Study (Safety Population, N=785)

Clinical Adverse Experience Summary (Safety Population, N=785)								
	ALL		Age < 65		Age 65-74		Age 75+	
	n=519		n=344		n=90		n=85	
With one or more adverse experience(s)	519	66.1%	344	43.8%	90	11.5%	85	10.8%
With drug-related adverse experience(s)	273	34.8%	197	25.1%	37	4.7%	39	5.0%
With serious adverse experience(s)	35	4.5%	21	2.7%	37	4.7%	39	5.0%
With serious drug-related adverse experience(s)	1	0.1%	0	0.0%	1	0.1%	0	0.0%
Deaths from serious drug-related adverse experience(s)	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Discontinued study drug then restarted (all reasons for stopping)	42	5.4%	29	3.7%	7	0.9%	6	0.8%
Discontinued study drug permanently (all reasons for stopping)	152	19.4%	105	13.4%	25	3.2%	22	2.8%
Discontinued study drug then restarted due to adverse	21	2.7%	19	2.4%	1	0.1%	1	0.1%
Discontinued study drug permanently due to adverse experiences	110	14.0%	79	10.1%	18	2.3%	13	1.7%
Discontinued study drug due to serious adverse experiences	13	1.7%	9	1.1%	3	0.4%	1	0.1%
Serious drug-related adverse experiences	1	0.1%	0	0.0%	1	0.1%	0	0.0%
Lost to Follow-up								

Please see the review of the medical officer for details of the safety evaluation.

7 SUMMARY AND CONCLUSIONS

7.1 Statistical Issues

There is no statistical issue for this submission.

7.2 Collective Evidence

For the pivotal label comprehension study (protocol #10053), for the general population cohort:

Of the six communication objectives with higher medical consequence, two endpoints exceeded the pre-defined 90% threshold for success -- the lower bound of the 95% confidence interval (CI) was above 90%: allergic to oxybutynin (95.1%, [95% CI: 92.8%, 96.9%]) and allergic reaction to the patch (93.2% [95% CI: 90.6%, 95.3%]). Three endpoints were within 5 points of the threshold: urinary retention (91.3% [95% CI: 88.4%, 93.7%]), gastric retention (89.9% [95% CI: 86.7%, 92.4%]) and developed blisters and red, itchy skin (88.6% [95% CI: 85.3%, 91.3%]). The endpoint related to narrow angle glaucoma missed the threshold by 5.6 points (87.7% [95% CI: 84.4%, 90.5%]).

Of the communication objectives with lower medical consequences, one endpoint exceeded the pre-defined 85% threshold: kidney stones (89.8% [95% CI: 86.7%, 92.4%]). Three endpoints were within 5 points of the threshold: have OAB symptoms for at least 3 months (87.3% [95% CI: 83.9%, 90.2%]), using a diuretic (87.1% [95% CI: 83.7%, 90.0%]) and liver disease (83.9% [95% CI: 80.3%, 87.1%]). Finally, for stress incontinence, the point estimate was 77.3% with 95% CI of [73.3%, 81.0%].

For the women aged 44+ with diabetes risk factors cohort: Both of the primary objectives related to the diabetes warnings were within three points of meeting the 85% threshold (History of diabetes: 88.8% [95% CI: 82.8%, 93.2%]; Diabetes symptoms: 88.1% [95% CI: 82.1%, 92.7%]).

For the actual use study CL2008-13, post mitigation, the proportion of subjects who did not stop use when they either developed a new symptom referred to anywhere in the label or when their condition worsened including abdominal and/or pelvic pain was 3.4% (25/727) with 95% CI of (2.2%, 5.0%). The upper bound of the confidence interval meets the pre-defined target threshold of 5%.

In the actual use study CL2008-13, of the 1069 subjects who made an Oxytrol purchase decision, 839 subjects (78.5%) made a positive purchase decision and had ineligibilities according to the label.

7.3 Conclusions and Recommendations

The statistical reviewer does not identify any statistical issues that may preclude the approval of this NDA. However, as the clinical implication of such high label ineligibility rate (78.5%) is beyond the scope of statistical evaluation, the statistical reviewer defers the decision of approval of this NDA to the clinical team.

SIGNATURES/DISTRIBUTION LIST

Yunfan Deng, Ph.D.
Primary Statistical Reviewer

Concurring Reviewer:

Yan Wang, Ph.D
Statistical Team Leader:

cc:

HFD-520/Project Manager: Phong Do

HFD-520/Medical Officer: Ryan Raffaelli, M.D.

HFD-520/Medical Team Leader: Lesley-Ann Furlong, M.D.

HFD-725/Primary Statistical Reviewer: Yunfan Deng, Ph.D.

HFD-725/Statistical Team Leader: Yan Wang, Ph.D

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/s/

YUNFAN DENG
11/16/2012

YAN WANG
11/16/2012
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202211	Applicant: Merck Consumer Care, Inc. (MCC)	Stamp Date: March 26, 2012
Drug Name: OXYTROL for Women Oxybutynin Transdermal System, 3.9 mg/day	NDA/BLA Type: NDA, Standard Review	Indication: Relief of overactive bladder symptoms

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	✓			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).		✓		Comment #1

We consider the statistical section of the application fileable. However, the following issues are noted.

1. At the pre-NDA meeting, we requested the data format for the actual use study (CONTROL) including the following flag variables for each type of conditions stated in the label:
 - Condition worsens
 - New symptoms appear
 - Condition does not improve after 2 weeks of use
 - Having an allergic reaction to the product
 - Having severe redness, itchiness, or blistering at the site of application

However, we have difficulty locating these variables in the primary efficacy dataset ADEP1.

2. Although the applicant's analysis results for the primary and key secondary endpoints can be reproduced following the instructions provided in the submission, it is very difficult to understand how the results were derived from the program codes. The review of the actual use study would be difficult since the dataset structure is difficult to understand and interpret.
3. The datasets for all the label comprehension studies and self-selection studies were submitted, however the applicant did not submit the program codes used to produce the primary efficacy results for these studies.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			✓	
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			

Statistical Information Request:

1. Please resubmit the primary efficacy dataset ADEP1 with the following 24 flag variables (12 for pre-mitigation and 12 for post-mitigation) included:
 - One flag for “condition worsens” and one flag indicating whether the user stops use or not when the condition worsens
 - One flag for” new symptoms appear” and one flag indicating whether the user stops use or not when new symptoms appear
 - One flag for “condition does not improve after 2 weeks of use” and one flag indicating whether the user stops use or not when the condition worsens
 - One flag for “having an allergic reaction to the product” and one flag indicating whether the user stops use or not when having an allergic reaction to the product
 - One flag for “having severe redness, itchiness, or blistering at the site of application” and one flag indicating whether the user stops use or not when having severe redness, itchiness, or blistering at the site of application
 - One flag for “having abdominal and/or pelvic pain” and one flag indicating whether the user stops use or not when having abdominal and/or pelvic pain

Please use the following format: 1 for Yes, 2 for No, and 99 for Missing for these variables. Please also submit the program codes used to derive these variables. We expect that these program codes will help us understand how the primary and key secondary endpoints are derived, and the derived variables will enable us to reproduce your results presented in Table 13, 14, 16, 18, and 20 of the study report and perform supportive analyses if needed during our review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

2. Please submit the program codes used to produce the primary efficacy results for all the label comprehension and self-selection studies.

Yunfan Deng

Reviewing Statistician

Date

Yan Wang

Statistical Team Leader

Date

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/s/

YUNFAN DENG
04/26/2012

YAN WANG
04/26/2012