In February 2012, the US Food and Drug Administration (FDA) announced the Rx-to-OTC switch approval of oxybutynin in the form of Oxytrol® Transdermal System for women suffering from overactive bladder (OAB). This regulatory decision is a potentially important advance in self-care that may fill the gap in undertreatment of OAB in the U.S. Furthermore, the switch decision carries with it regulatory science implications for how FDA undertakes benefit-risk assessments for switch, especially in light of the agency's recent publication of its structured qualitative descriptive approach to pharmaceutical benefit-risk decision making. This paper includes an introductory perspective of the potential significance of OAB as an OTC indication, an overview of the pivotal dataset supporting the switch of transdermal oxybutynin to OTC status, and a discussion of FDA's qualitative descriptive approach to benefit-risk in the context of Rx-to-OTC switch.

Key words: Rx-to-OTC switch, Benefit-Risk, Oxybutynin, Oxytrol TDS, overactive bladder

POTENTIAL SIGNIFICANCE OF OAB AS AN OTC INDICATION

OAB Prevalence

Based on population studies, the prevalence of OAB is estimated to be about 16% in the U.S. and EU, and Canada. In relation to other diseases, OAB is one of the most common chronic diseases in the US, affecting an estimated 13 million Americans and being more prevalent than ulcer (4 million) and diabetes (9 million). The broader symptom complex of OAB is likely more prevalent than asthma (15 million) and/or heart disease (33 million) and chronic sinusitis (37 million).

Definition of OAB

The International Continence Society (ICS) Standardization Subcommittee defines overactive bladder (OAB) as a symptom syndrome suggestive of lower urinary tract dysfunction which is characterized by urgency, with or without urge incontinence, usually with frequency (>8 voids/day) and nocturia (>1 time/night) in the absence of infection or other irritative lesions. ICS classifies OAB as a syndrome for which no precise cause has been identified (idiopathic), with conditions that may cause or mimic OAB ruled out by diagnostic evaluation. OAB
is the result of involuntary contractions of the muscles surrounding the neck of the bladder more frequently than normal, at inappropriate times, and often when the bladder is only half full instead of three-quarters full or more. A person perceives OAB-related involuntary bladder contractions as an urgent need to urinate. A person with ‘dry’ OAB may make it to the bathroom on time but not without worry and anxiety. A person with the ‘wet’ form of OAB may not always make it without leaking urine, compounding worry and anxiety with embarrassment.

Causes of OAB

An overactive bladder is typically due to improperly functioning bladder muscles or nerves creating the urgent need to urinate. Two conditions tend to occur: the urinary sphincter remains constricted and prevents the bladder from leaking; or the sphincter’s ability to perform is limited by the contraction resulting in urge incontinence – or leaking. Several medical conditions can be the source of OAB and symptoms of OAB have many causes, as shown below in Table 1. However, in most cases the exact causes of OAB cannot be found.

Table 1. Causes of Symptoms of OAB & Common Triggers of OAB

<table>
<thead>
<tr>
<th>Causes of OAB</th>
<th>Common Triggers (Factors Increasing Urge to Urinate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bladder and urinary tract infections</td>
<td>• Acidic food and beverages, like orange juice and tomatoes</td>
</tr>
<tr>
<td>• Bladder cancer, or other abnormalities of the bladder (e.g., bladder outlet obstruction)</td>
<td>• Alcohol</td>
</tr>
<tr>
<td>• Bladder outlet obstruction due to previous surgery for incontinence</td>
<td>• Artificial sweeteners</td>
</tr>
<tr>
<td>• Bladder stones</td>
<td>• Coffee and other caffeinated drinks</td>
</tr>
<tr>
<td>• Depression, anxiety, or attention deficit hyperactivity disorder (ADHD),</td>
<td>• Constipation</td>
</tr>
<tr>
<td>according to some experts may predispose individuals to OAB.</td>
<td>• Drinking too much – or not enough – fluids</td>
</tr>
<tr>
<td>• Diabetes</td>
<td>• Spicy food</td>
</tr>
<tr>
<td>• Fibromyalgia (i.e., a condition with symptoms of muscular pain and fatigue</td>
<td>• Cold weather</td>
</tr>
<tr>
<td>inflammation or enlargement of the prostate or prostate cancer</td>
<td>• Emotional distress</td>
</tr>
<tr>
<td>• Irritable bowel syndrome (i.e., a condition with symptoms of abdominal pain,</td>
<td></td>
</tr>
<tr>
<td>bloating, and constipation or diarrhea, or both)Kidney disease</td>
<td></td>
</tr>
<tr>
<td>• Nerve damage caused by previous surgeries or trauma or by trauma to the</td>
<td></td>
</tr>
<tr>
<td>abdominal area or pelvis or prior surgery</td>
<td></td>
</tr>
<tr>
<td>• Neurological conditions, including: stroke, Parkinson’s disease, cerebral</td>
<td></td>
</tr>
<tr>
<td>palsy, multiple sclerosis, transverse myelitis; spinal cord injuries</td>
<td></td>
</tr>
<tr>
<td>• Side effects from medications, especially diuretics (water pills) and drugs with caffeine (see also OAB Triggers below)</td>
<td></td>
</tr>
</tbody>
</table>
Quality of Life Impact

OAB is associated with significant physical and psychosocial distress, and treatment is not always successful. Milsom et al. estimate that about 66% of people (men 65% and women 67%) with OAB report that their symptoms affect their daily living. Of these, 60% with symptoms find them bothersome enough to consult a medical practitioner.

Frequency and urgency alone (59%) are almost as common as urge incontinence (66%) as reasons for seeking medical help. Lieberman et al. conducted a US cross-sectional household telephone survey in an age-stratified sample of 4,896 adults; a follow-up questionnaire was mailed to a subset of these respondents to assess their health-related quality of life (HRQOL) related to OAB. After adjustment for confounders, both groups (OAB wet and OAB dry) had significantly lower crude HRQOL scores than the control groups in every domain. Statistically significant differences were observed in five of the six domains for the total OAB group, all six domains for the OAB wet group, and three of six domains for the OAB dry group. In the OAB dry group, after adjustment for confounders, individuals with symptoms of both frequency and urgency scored statistically significantly lower than did the controls in all six HRQOL domains.

In a large US epidemiologic study, illness impact was assessed by completed self-administered questionnaires on quality of life, depression status, and sleep quality. After adjusting for differences in comorbid illnesses and other demographic factors, both men and women with OAB wet and OAB dry had clinically and significantly lower quality-of-life subscores, more depression-related symptoms, and a poorer quality of sleep. Other studies support the results of the large epidemiologic reports. In particular, the study by Abrams et al. and the review by Ellsworth and Kirschenbaum share insights into the how consumers and patients talk about the quality of life limitations imposed by symptoms of OAB. These clinicians report that patients with OAB may report: a loss of self-esteem; guilt; fear being a burden to their family and friends; fear the odor of urine; decrease in social interactions; limits on travel to areas where a known bathroom is nearby; use of specialized underwear, protective bedding, and dark, bulky clothing to hide the protective undergarments; limits on sexual relationships, sexual contact and intimacy for fear of leakage or the odor of urine. There are also other co-morbidities associated with OAB including: increased risk of falls and fractures; increased skin infections; higher risk of hospitalization for those with UUI (30% increased risk for women and 50% increased risk for men) and a higher likelihood for an older adult with UUI to be admitted to nursing homes; and depression.

Undertreatment of OAB

While OAB is associated with significant physical and psychosocial distress, many patients are reluctant to seek medical help for OAB and urinary incontinence. The social stigma borne by the wet patient, along with the misconception that urinary incontinence is a normal consequence of aging, contribute to the reluctance of patients to seek help.

Yet, when patients seek treatment, only a small percentage receive medication. Among those seeking medical care, only 27% were receiving medication for symptoms at the time of the
interview. Of those who were not taking medication, 27% reported that they had previously tried pharmacologic treatment, which failed. About 54% of those who had never tried drugs reported that they were likely to discuss the problem with a physician again. Among those who had tried drugs but in whom the drugs had failed, 65% reported that they were likely to discuss the problem with a physician again and 35% were not.

Reports of OAB as an undertreated condition do not always explore the underlying reasons. Treatment failure with OAB medications is relatively high. Persistence with antimuscarinic therapy has been documented as poor\textsuperscript{25,26}. For example, in a recent analysis of withdrawal rates based on prescription data, in almost 20,000 patients receiving treatment for OAB with oxybutynin or tolterodine as immediate or extended release products, fewer than 20\% of patients were still taking their medication after 1 year\textsuperscript{27}.

OVERVIEW OF THE PIVOTAL DATASET SUPPORTING THE SWITCH OF TRANSDERMAL OXYBUTYNNIN TO OTC STATUS

Oxybutynin

Oxybutynin is an anticholinergic medication approved for use in relieving urinary and bladder problems relating to urinary frequency and control (urge incontinence). Oxybutynin decreases bladder muscle spasms through competitive inhibition of M1, M2 and M3 muscarinic receptors. The transdermal patch applied twice a week delivers 3.9 mg/day. The patch was approved for prescription use on February 26, 2003 with the indication: ‘For the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency’\textsuperscript{28}. Prescription oxybutynin is also available as a gel, syrup and tablets. Other antimuscarinic agents available as Rx products in the US are: darifenacin; fesoterodine; solafenacin; tolterodine; trospium. Mirbetryl is a beta-3 adrenergic receptor agonist also available in the US.

The OTC transdermal version of oxybutynin (trade name, Oxytrol\textsuperscript{®}) was approved on January 25, 2013 for treatment of overactive bladder in women, with availability projected in stores in September 2013\textsuperscript{29,30}. Complete materials from FDA and company presentations is available on the FDA website under ‘Advisory Committees/Nonprescription Drug Advisory Committees’\textsuperscript{31,32}.

Rx-to-OTC approval was supported by the NDA pivotal studies – i.e., two Phase 3 placebo-controlled randomized, double-blind clinical trials of 12-week duration. One pivotal trial assessed three doses of Oxytrol\textsuperscript{®} vs. placebo (including the 3.9 mg/day dosage); the other, Oxytrol\textsuperscript{®} at 3.9 mg/day vs. tolterodine and placebo. Primary endpoints were: change from baseline in number of weekly incontinence episodes and change from baseline in number of daily incontinence episodes. Primary endpoints showed statistical significance for active drug at the first on-treatment visit, with efficacy maintained through 12 weeks.

The clinical trial safety database was also supported by 16 Phase 1, one Phase 2 and two Phase 3 clinical studies from the NDA. Overall, about 600 subjects were exposed for periods of
1-428 days with the average exposure 150 days. The rate of side effects above 1% are shown in Table 2, with anticholinergic side effects (e.g., drug mouth and constipation) and application site pruritus being the most commonly reported adverse experiences in the clinical study population. During the November 2012 FDA Advisory Committee on the switch of Oxybutynin, the FDA medical officer concluded: ‘No safety issues were identified that precluded Oxytrol® TDS approval [for OTC availability]’.

Table 2: Summary of Adverse Events Seen in >1% of Subjects in the Phase 3 Trials for the Rx Product

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Number of Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Containing TDS (n=249)</td>
</tr>
<tr>
<td>Application Site Pruritus</td>
<td>13 (5.2%)</td>
</tr>
<tr>
<td>Application Site Erythema</td>
<td>5 (2.0%)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>13 (5.2%)</td>
</tr>
<tr>
<td>Application Site Vesicles</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Abnormal Vision</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

The evidence base for OTC availability of transdermal oxybutynin was augmented with additional consumer studies, including self-selection, label comprehension and actual use studies. Label comprehension studies were undertaken in normal and low literacy individuals using both 90% and 85% comprehension criteria cutoffs for the general higher-health literacy population, depending on the communication objectives. Key concerns related to consumer self-recognition of OAB, urinary/gastric retention, diabetes risk, UTI, pregnancy women, men and the elderly. The development of the final proposed OTC label and pivotal label comprehension study was a typical iterative process, well described in the transcript of the meeting.

The in-use (‘actual use’) consumer study was a 15-week, open-label, single-arm, multicenter trial involving 26 pharmacy sites in ten metropolitan areas, to assess use and misuse of the product with the proposed labeling by women 18 years and older. This was an ‘all comers’ study, which included women who did not meet all of the eligibility criteria from the proposed label. Recruitment was by mass media advertising. The primary endpoint was the proportion of subjects who did not stop Oxytrol® use either when they developed a new symptom where the label directed them to stop use or talk with a doctor or when their OAB condition worsened. A successful study outcome was defined as a misuse rate of 5% or less. The secondary endpoints were no improvement of OAB symptoms after two weeks, and incorrect use by prolonged duration (> 4 days) or simultaneous use of more than one TDS. Common to analytical plans for most actual use studies, a mitigation strategy was used to adjudicate the raw findings with a
judgment of correct use if the potential misuser displayed medically acceptable behavior. After mitigation, 96.6% of subjects were assessed as having shown correct behaviors, meaning 3.4% displayed misuse, which was below the predefined rate of 5%. (For more in-depth information on study results for the consumer studies, see the meeting materials for the November 9, 2012 advisory committee meeting. See also the Appendix for a more detailed description of consumer studies).

Postmarketing safety data from the FDA Adverse Experience Reporting System (AERS), the World Health Organization, and the American Poison Control Centers also supported the transdermal oxybutynin switch. Since 2004, 13,700 adverse experiences were reported in the sponsor’s database, on a base of over 40 million Oxytrol® Transdermal Systems distributed. Approximately 96% of all reports were non-serious, 0.7% were classified as serious and were already contained on the approved Rx label. Almost 40% of all reported adverse events related to application site reactions.

In summary, the evidence-base for OTC Oxytrol® Transdermal System included the usual type of consumer studies, and, although not shown, the criteria for acceptable safety were similar to criteria used for Rx-to-OTC switch decisions in the past.

DISCUSSION OF OTC REGULATORY SCIENCE IMPLICATIONS

Several specific and broader-reaching regulatory science implications of the OTC oxybutynin approval are elaborated below.

First, Oxytrol® is the first OTC treatment of overactive bladder. OAB is a prevalent chronic condition with negative quality of life consequences of importance to consumers. On this basis one would expect transdermal oxybutynin to be an important addition to the armamentarium of nonprescription medicines. A close watch of the longer-term marketing success will determine the impact from the relatively high rate of adverse application site reports, and the extent of long-term adherence to the OTC version of a medicine for OAB control in the context of alternative reimbursed Rx antimuscarinics, the high discontinuation rate for Rx antimuscarinics, and the impact of future generic competition in expanding the market access to consumers.

Second, the indication is limited to women 18 years of age and older, thereby overcoming concern about a potentially significant hurdle of misdiagnosis of prostate disorders (including cancer) had the company sought approval for men as well.

Third, the clinical plan developed by Merck was well executed and followed the basic framework of prior Rx-to-OTC clinical development strategies by various companies. The scope and nature of questions to the advisory committee are in line with the types of questions that have been used to focus the Nonprescription Drugs Advisory Committee on the essential safety, effectiveness and communication issues relating to Rx-to-OTC switch. For regulatory scientists, a review of the designs, methodologies and outcomes of the consumer studies (i.e., self-selection, label comprehension and actual use) can provide a clear understanding of the
current type of studies and the benchmarks for acceptable outcome thresholds needed for future Rx-to-OTC drug approval in chronic disease categories.

Fourth, the briefing materials prepared by FDA were comprehensive, particularly the description of the consumer studies as one of the key components of the Rx-to-OTC drug application. As part of these materials, FDA prepared a general treatise on framework and design of consumer studies for the advisory committee considering transdermal oxybutynin. This represents a very clear, comprehensive perspective of the basis for OTC access to medicines in the United States at the current time. (The relevant section is reproduced as an appendix to this paper).

Finally, shortly after FDA announced the approval of Oxytrol® Transdermal System, the agency issued a call for comments on its description of a ‘Structured Approach to Benefit-Risk Assessment in Regulatory Decision-Making’. FDA’s stated approach has important implications for all aspects of drug development and postmarketing surveillance. As a foundation, US drug law does not explicitly define how a benefit-risk determination is to be made for a drug product. Over the years there have been suggestions that a more quantitative approach might be taken to provide a better framework and predictability to the drug assessment process.

In the last few years, as other disciplines such as decision science and health economics have been applied to drug regulatory decision-making, there has been much discussion among regulators, industry, and other stakeholders regarding “qualitative” versus “quantitative” approaches to benefit risk assessment. The term ‘quantitative benefit-risk assessment’ can have various meanings depending on who is asked. Some hold the view that a quantitative benefit-risk assessment encompasses approaches that seek to quantify benefits and risks, as well as the weight that is placed on each of the components such that the entire benefit-risk assessment is quantitative. This approach is typical of quantitative decision modeling. It usually requires assigning numerical weights to benefit and risk considerations in a process involving numerous judgments that are at best debatable and at worst arbitrary. The subjective judgments and assumptions that would inevitably be embodied in such quantitative decision modeling would be much less transparent, if not obscured, to those who wish to understand a regulator’s thinking. Furthermore, application of quantitative decision modeling seems most appropriate for decisions that are largely binary. Many benefit-risk assessments are more nuanced and conditional based on parameters that could be used to effectively manage a safety concern in the post-market setting. There is significant concern that reliance on a relatively complex model would obscure rather than elucidate a regulator’s thinking.

These concerns have led FDA to the conclusion that the best presentation of benefit-risk considerations involves focusing on the individual benefits and risks, their frequency, and weighing them appropriately. FDA believes that this can be accomplished by a qualitative descriptive approach for structuring the benefit-risk assessment that satisfies the principles outlined earlier in this section, while acknowledging that quantification of certain components of the benefit-risk assessment is an important part of the process to support decision-making.
FDA considers it most important to be clear about what was considered in the decision, to be as quantitative as possible in characterizing that information, and to fully describe how that information was weighed in arriving at a conclusion. Quantitative assessments certainly underpin the qualitative judgments of FDA’s regulatory decisions, but FDA has adopted a structured qualitative approach that is designed to support the identification and communication of the key considerations in FDA’s benefit-risk assessment and how that information led to the regulatory decision.” (Excerpt from page 4 of reference 38)

In the context of self-care with OTC medicines, FDA thus supports its long-standing approach to drug benefit/risk decision-making as a qualitative descriptive approach. This is reflected in the recent publications in SelfCare on detailed assessments of FDA’s switch decision-making process for first in class switches (references 36 and 37). FDA’s structured descriptive approach defines three key areas (i.e., Analysis of Condition and Current Treatment Options; Benefit and Risk; Risk Management) with two domains within each (i.e., Evidence and Uncertainties; and Conclusions and Reasons). FDA’s structured approach is currently open for public comment. Those who may favor a more quantitative approach to drug assessments have a high hurdle to overcome, based on the work and thoroughness of thought that the agency has applied to articulating its long-standing framework on benefit-risk. On the assumption that this basic benefit-risk structure becomes widely accepted, a practical implication will be the likely revision of how sponsors will be asked to interpret efficacy, effectiveness and safety data in their Rx and Rx-to-OTC drug applications. The scope, nature and quality of sponsor presentations to advisory committees will also likely change in a conforming way.

CONCLUSION

The Rx-to-OTC switch of Oxytrol® Transdermal System represents a significant regulatory advance in the potential expansion of access to a medicine approved for control of overactive bladder. How this regulatory advance will translate into meaningful advances in population-based self-care remains to be seen, as is true for any just-approved Rx-to-OTC switch. A key question is, how will consumers balance the high rate of application site reactions and non-covered out-of-pocket long-term expenditure against the important quality of life benefits that the medicine offers?

On a higher level, the approval of Oxytrol® Transdermal System is a clear expression of FDA’s qualitative descriptive approach to benefit-risk assessment through the standard triad of consumers studies – self-selection, label comprehension, and actual use. This approach has been articulated recently by the agency in its published call for public comment, and will likely have important implications for how companies reframe their drug development plans and their presentations of drug outcome data in both new drug applications and in advisory committee meetings.

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APPENDIX


A consumer who uses an OTC product is making his or her own healthcare decision without a healthcare provider intermediary. Consumer studies can support OTC approval of a drug product by showing that consumers are able to understand the product label and can appropriately self-select, and self-medicate for a particular condition in an OTC environment using only the OTC drug label.

This overview will summarize the general characteristics of three types of consumer behavior studies, Label Comprehension Studies (LCS), Self-Selection (SS) and Actual Use Studies (AUS). Data from these studies provide information about how well an over-the-counter (OTC) product label can inform the nonprescription drug consumer about the drug and whether the consumer can appropriately use the information on the label. Thus, these data play a major role in helping to determine whether a product should be marketed without a prescription.

The prescription to OTC switch process is guided by federal regulations. The Federal Food, Drug, and Cosmetic Act Sec. 201. (321) (g)(1) states that the term “drug” means articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease and intended to affect the structure or any function of the body of man. The Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act draws a distinction between prescription and non-prescription drugs. This distinction is stated in the Code of Federal Regulations 21 CFR 310.200(b) as follows:

“Any drug limited to prescription use under section 503(b)(1)(C) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug’s toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling.”

When a drug that has been previously available only by prescription is switched to OTC status, the healthcare provider is no longer a gatekeeper to drug access. Thus, drug labeling must communicate directly to the consumer. The consumer must understand and act appropriately based on the information available in OTC labeling.

While the general structure of the OTC drug label is codified in the Code of Federal Regulations, the text used to communicate to consumers undergoes iterative study and optimization. (See Appendix 2 – Proposed Nonprescription Labeling for oxybutynin TDS, for an example of a “Drug Facts” OTC label.) Labeling used in LCS, SS, and AUS studies evolves, and the final product labeling ideally reflects the lessons learned from consumers following a careful label development program.

The development program for oxybutynin TDS was an iterative process that involved LCS, SS, and AUS. Proposed labeling for oxybutynin TDS includes the principal display panel and Drug Facts section required by regulation. (See Appendix 2 – Proposed Nonprescription Labeling.)

Label Comprehension Studies (LCS):

It is important to study whether consumers can understand the information on a product label, particularly when new OTC indications, directions for use, and new warnings are contained therein. LCS can help to develop labeling that communicates effectively.

The study is a critical element to the label development process for an OTC drug. If a study succeeds, it can at least assure that respondents understand the label that is used in the Actual Use Study, and this label will be similar, if not identical, to the label that accompanies the product to market. If the results suggest that certain elements are not understood, the study can still be contributory as long as information is collected to help establish the reasons for the errors. The LCS results may not accurately predict consumer behavior, such as self-selection, purchase decisions, or adherence. (It is important to note that, for the oxybutynin TDS application, the sponsor conducted the pivotal LCS and the AUS simultaneously using the same label; therefore, the label used in the AUS did not reflect information derived from the pivotal LCS.)
LCS should have a series of key communication objectives, (the information that it is important to convey to the consumer). LCS can test how well consumers comprehend the information displayed on the outside of the drug carton, contained inside the package (inserts), and any other crucial informational material. The investigators should ascertain why participants who answer incorrectly, answer the way they do so that this information can improve the label. The label development process is ideally an iterative one. If the tested label does not communicate the important medical messages adequately, the labeling can be revised and another LCS performed.

Label comprehension studies can be useful under many different circumstances, including the following, all of which apply to the oxybutynin TDS switch to OTC:

- The drug is the first in its class to enter the OTC market;
- The drug targets a new OTC population;
- There is a new OTC indication.

**Study Design:**

The label comprehension study is a study in which no drug is administered. Study participants (respondents) read the label to be tested. Trained investigators administer a questionnaire (the study instrument) using scripted interactions with the respondent.

Generally respondents are given unrestricted time to read the label and can refer back to it during the testing. The purpose of the testing is to assess comprehension, not memorization.

**Target Population:**

We try to obtain an LCS target population that is representative of the United States population of potential product users and nonusers. To attract this target population, tests have been administered in shopping malls and other purchase sites that are demographically diverse.

The general population is often enriched with subgroups of special interest, for example, those of a particular gender, age, race, sex, or those with a medical condition that would put them at high risk if they took the drug. The populations have included a low literacy cohort, generally identified by the score on the Rapid Estimate of Adult Literacy in Medicine (REALM) test. This test was used to identify low literacy cohorts for the Oxytrol TDS consumer studies.

**Questionnaire:**

The main data collection tool for a LCS is the consumer Questionnaire. The questionnaire should be designed to reflect the communication objectives of the study. The wording of the questionnaire, the order of questions, and the structure of the questions can affect the results of the study by not gathering the appropriate information, introducing respondent fatigue, or by introducing bias.

There are many types of questions that have been used and each has advantages. Openended questions allow the respondent to give an unrestricted answer that can be recorded verbatim. Closed-ended questions offer the opportunity for the respondent to choose from among a restricted answer set as in a multiple choice question. Scenarios are questions that require the respondent to apply information from the label to respond correctly. A scenario question consists of a brief description of a medical situation. The respondent responds to a question about whether, in this situation, the product would be appropriate to use. Scenario questions can provide very informative data and may offer a window into the ability of respondents to use the product properly. They are being used commonly in LCS because they require not just the comprehension of information, but the ability to process it.

Information from one question should not influence the responses to subsequent questions. It is important that multiple choice questions be mutually exclusive and that they not contain language that participants may interpret as a “safe” answer. They should not contain a default answer such as “ask a doctor” unless asking a doctor is the correct answer according to the label.

**Analysis:**

It is important to note that adequate label communication is an issue of clinical judgment and varies depending upon the medical significance of a particular communication objective. Different healthcare professionals may have different thresholds for adequacy and thus this often has become a matter of discussion.
Results for each communication objective have been analyzed by the general population and by specific subgroups to determine the percentage of correct responses. We often make a decision based on the lower bound of the 95% confidence interval around the point estimate of correct responses for comprehension. Typically, this point estimate is compared with a pre-specified target threshold for success that is supported by a clinical rationale. Determining pre-specified targets for success is difficult and not a very rigorous scientific process.

It is common that the low literacy cohort (those who read at less than an eighth grade level) does not perform as well as the normal literacy cohort. You will see that this was true for the Oxytrol TDS consumer data. Determining what is an acceptable difference in label comprehension between the normal and low literacy cohorts is a challenge.

**Self-Selection Studies (SS):**

Self-selection data are collected to determine if a consumer can, after reading the product label, make a correct decision about whether or not the product is appropriate for him/her to use based upon the indications and warnings. SS should assess the ability of a consumer to correctly self-diagnose the condition for which a product is indicated and determine whether the product is appropriate for them to use. No drug is administered during a self-selection study. Sometimes self-selection data are collected as part of an actual use study; sometimes as part of an LCS study and sometimes as a stand alone study. For the Oxytrol application, three self-selection studies were conducted and self-selection information was also available indirectly from an actual use study (see below) related to purchase decisions that study participants made. Self-selection was not a primary or secondary endpoint in the actual use study.

**Study Design:**

The target population of the SS should be potential users of the product some of whom could use the product and some of whom should not use the product. Study participants review the product label and are asked a self-selection question to which they respond. In one self-selection study for the oxybutynin TDS application, the self-selection question was, “Do you feel that this product is right for YOU to use?” Validating the self-selection response is important. Clearly, it is important to understand why consumers self-select incorrectly. Alternatively, perhaps what appears to be an error is really medically acceptable for the individual and mitigation can be considered in the analyses based upon this circumstance. Other areas that need attention with regard to the self-selection study design are:

- The best wording for posing the self-selection question so it will not influence how people may respond to it;
- The appropriate way to assess self-selection in subpopulations at risk for using the drug.

The acceptability of the success rate for pivotal issues related to self-selection for an OTC product and the acceptability of the failure rate is often the topic of debate. For example, when should the majority who could benefit from access to an OTC drug be denied that access because of self-selection errors made by a small subpopulation that could be at risk for using the drug? How significant are the clinical consequences of not heeding a specific labeling message?

**Analysis:**

SS typically provide a point estimate and a 95% confidence interval around the point estimate of correct response for self-selection. The calculation of the point estimate is pre-specified in the protocol, and the acceptable target threshold is ideally supported by a sound clinical rationale. Interpreting data when multiple selection criteria are required for correct self-selection can be complicated.

**Actual Use Studies (AUS):**

In an actual use study participants actually take the study drug home and may use it, so, unlike an LCS or SS, an AUS is a clinical trial. The purpose of an actual use study is to simulate the OTC use of a product. Hopefully, the AUS can provide meaningful consumer data so we can attempt to predict if a drug will be used properly, safely, and effectively in the OTC setting. Examples of things an actual use study can assess are:

- Adherence (taking the drug and performing any monitoring for efficacy and safety in accordance with the drug label);
- Safety (adverse events that occur during the study);
- Efficacy (whether the clinical benefit in the prescription setting is reproduced in the OTC setting). This seldom has been done (and was not done for oxybutynin TDS). AUS can assess the ability of the consumer
to use the product for the indicated purpose (self-treat) and can also assess whether consumers are abusing or misusing, the study drug. Some issues that might trigger the need for an actual use study include:

- New OTC indication;
- New method of use for an OTC drug;
- New OTC warnings;
- New OTC medical follow-up requirements or recommendations;
- Specific concerns about self-selection or de-selection.

**Study Design:**

The design of an AUS can vary. Usually AUS have been single-arm, multi-center, uncontrolled, open-label studies (the oxybutynin TDS CONTROL study is an example of this design). An AUS should be performed in a venue that simulates, as closely as possible, the true OTC environment. It is clear that a truly “naturalistic” environment cannot be perfectly achieved; data need to be collected. However, if no clinical sites are used, if the study participant can purchase study drug without restriction, and if there is no unsolicited healthcare provider involvement, a study can come close to simulating a real nonprescription purchase setting. Study elements that limit the naturalistic setting are the informed consent form, data collection tools like diaries which can serve as memory prompts to the study participant, and any other educational tools that may not be carried over into the true OTC setting. When study elements that limit the naturalistic setting are used in the AUS we cannot be certain that the same level of safety and efficacy will be achieved if the consumer uses the product without these additional elements. This issue is always considered when we provide comments to a sponsor about their AUS study design. Ideally, all consumers who have an interest in the product should be the target of recruitment efforts. It is also reasonable to recruit targeted subgroups of interest (e.g., low literacy, specific demographics, and medical conditions). These subgroups can provide more information about the potential safety (or efficacy) concerns.

We grapple with what an acceptable success rate is for pivotal issues related to actual use for an OTC product. Acceptable error depends upon the specific drug, specific indication, and safety concerns. Consideration needs to be given to how we should make decisions on approval of a drug when a small percentage of users could potentially be harmed by inappropriate use, but, on the other hand, a large percentage of users may benefit.

**Analysis:**

The number of study participants enrolled has varied with each drug and situation. Among the factors that could influence the number would be the incidence of the condition, the drug risks, and the cohorts. As with the LCS and SS, data have been presented for AUS as a point estimate of correct response. The point estimate is compared to a pre-specified target threshold, whose acceptability should be supported by a sound clinical rationale.