



## Consumer Healthcare Products Association

Briefing Book  
For the Meeting of the FDA Drug Safety and Risk Management Committee  
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## Introduction

In the May 4, 2010, *Federal Register*, the Food and Drug Administration announced a meeting of the Drug Safety and Risk Management Advisory Committee to discuss the abuse potential of dextromethorphan and the public health benefits and risks of this ingredient as a cough suppressant. FDA noted the Department of Health and Human Services received a request from the Drug Enforcement Administration for a scientific and medical evaluation and scheduling recommendation for dextromethorphan.

The Consumer Healthcare Products Association (CHPA) is the national trade association representing manufacturers and distributors of OTC medicines and dietary supplements in the United States, including cough suppressants that contain the antitussive dextromethorphan. As such, we have an interest and expertise in the subject matter of the Advisory Committee meeting and are providing background information for the committee to review prior to the meeting.

### 1. Executive Summary

CHPA does not believe scheduling of dextromethorphan under the Controlled Substances Act is warranted. The prevalence and scope of reported abuse is limited. CHPA believes that there are more effective interventions to address OTC cough medicine abuse in general, and dextromethorphan abuse in particular, that preserve the significant public health benefit of consumer OTC access to these important cough medicines.

The materials in this briefing book cover the following areas:

- Regulatory review and description of the marketing authorization status of dextromethorphan;
- The need for access to over-the-counter dextromethorphan;
- Analysis of abuse potential;
- Reducing dextromethorphan abuse through evidence-based interventions;
- Recommendations on education, metrics, and congressional action; and
- Appendices covering:
  - Timeline of key events and interventions, 2003-2010;
  - CHPA interventions targeted against goals; and
  - Examples of successful educational interventions on inhalants and ecstasy

## **1.1 Regulatory Status and Market Data**

Dextromethorphan is a cough suppressant with a mechanism of antitussive action consistent with clinical cough relief. Dextromethorphan has a demonstrated safety profile as an OTC ingredient with over 50 years of safe, effective use under labeled conditions.

Dextromethorphan is the most widely used active ingredient to relieve cough. Dextromethorphan-containing OTC medicines account for 85-90% of all medicines containing a cough suppressant sold in the United States. Approximately 133 million package units of dextromethorphan-containing OTC medicines were purchased in the last year.

Originally approved by FDA as a cough suppressant in 1958, a review of the safety, effectiveness, and labeling of the ingredient was conducted through the FDA's OTC Review. At the time of the expert advisory panel's report, the panel noted abuse had been reported, but concluded the ingredient was generally recognized as safe and effective for OTC use and, "because of its low order of toxicity, it is probably the safest antitussive presently available" (FDA 1976). The final rule confirming dextromethorphan's status as generally recognized as safe and effective for OTC use was published in 1987.

Dextromethorphan is also present in a number of prescription medicines in combination with prescription-only ingredients, primarily promethazine.

## **1.2 Need for Access to OTC Dextromethorphan**

Self-care is an important part of today's healthcare system. OTC medicines play a vital role in America's healthcare system by providing ready access to medicines that can be used safely by consumers without the intervention of a healthcare professional. Access to OTC medicines enables consumers to take appropriate control of their own healthcare in many situations.

Acute cough is very prevalent in the general population, and multiple studies have demonstrated that the majority of Americans self-medicate for cough and the common cold. Dextromethorphan is the number one choice of consumers to relieve cough.

Cough relief is important since people's daily routines are significantly impaired when they suffer from acute cough. Cough results in nighttime sleep disruption, hoarseness, and, particularly in women over 45, urinary incontinence. These symptoms create a burden to individuals and they create an economic impact in terms of lost work days, school absenteeism, and reduced work productivity.

If consumers did not have access to dextromethorphan for self-care, a portion of the population would likely go to a healthcare provider to obtain a prescription medicine (including codeine and benzonatate-containing cough medicines) for their cough, thereby increasing healthcare costs to patients and the system at large. Requiring a physician visit would delay cough relief, increase the number of people with contagious respiratory viruses in the physician's office, and increase absenteeism at work and school.

### 1.3 Analysis of Abuse Potential

CHPA does not believe scheduling of dextromethorphan under the Controlled Substances Act is warranted. This conclusion is based on 50 years of marketing experience, consultation with experts, and the totality of a review of the data from pharmacology; preclinical and clinical studies related to its abuse liability; the prevalence of reported abuse from national, government-sponsored surveys; a review of outcomes databases; and dextromethorphan's benefits and risks to public health. There are more targeted, more effective, and less disruptive interventions than scheduling to address dextromethorphan abuse, while preserving consumer access to this important ingredient.

**Pharmacology:** Although structurally similar to other morphine derivatives, dextromethorphan is a non-narcotic cough suppressant. It does not act as an opioid receptor agonist, and it is devoid of morphine-like effects. It is believed to suppress cough by altering the threshold signal to cough initiation in the central nervous system.

**Abuse potential studies:** Clinical studies find that, at high doses (e.g., 8-20 times the maximum OTC dose), dextromethorphan can exert mixed clinical effects, eliciting both euphoria and dysphoria. These effects are often associated with nausea and vomiting, as well as "disliking" sensations in abuse liability evaluations. Dysphoria and "disliking" increase dose-dependently. These effects do not suggest potential for chronic abuse.

Withdrawal or tolerance do not appear to be factors in misuse and abuse of dextromethorphan. There are no controlled pre-clinical or clinical studies demonstrating that dextromethorphan produces physical dependence as measured by tolerance or withdrawal.

These clinical findings are consistent with qualitative research among substance abusers which shows little recurring abuse of dextromethorphan. Users describe the experience as unsatisfactory as a result of negative effects, including dysphoria, nausea, blurred vision, and disorientation.

**Prevalence of reported abuse:** National surveys show the abuse of OTC cough medicines, including those which contain dextromethorphan, is limited in its

prevalence and scope, with reported abuse concentrated in teens and, to a lesser degree, young adults. Prevalence is flat over the four years for which national data is available.

The low potential for abuse and low prevalence of abuse suggest that there are more effective interventions to reduce OTC cough medicine abuse while preserving the significant public health benefit of OTC access to dextromethorphan-containing cough medicines for consumers in need of treatment.

**Outcomes databases:** Databases which examine outcomes, including substance abuse treatment admissions or emergency room visits for non-medical use, reflect measurable but comparatively low levels of negative health outcomes from reported abuse.

**Risk and benefit to public health:** Dextromethorphan has a long history of use, and is well-tolerated when used as directed. Intentional abuse has been reported over time; however, the incidence of such abuse is low given its long history of widespread use. In general, health consequences of dextromethorphan abuse and resulting overdose appear infrequent and not serious, but can lead to morbidity, emergency room visits, and, in very rare instances, death.

The scheduling of dextromethorphan under the Controlled Substances Act would itself have a large *negative* public health impact by limiting access for those who have a need to relieve their cough. OTC access provides a public health benefit by allowing self-treatment of acute cough, saving doctor visits and prescription costs.

#### **1.4 Reducing Dextromethorphan Abuse Through Evidence-Based Interventions**

The OTC medicine industry, through CHPA, has an established history as a leader in developing long-term, evidence-based interventions to reduce and prevent the abuse of dextromethorphan and dextromethorphan-containing OTC cough medicines. The industry's efforts have evolved and grown over time as new data have been released. CHPA's goals, interventions, and assessments are informed by quantitative prevalence data, qualitative research into the abuser profile and behavior, and proven strategies and recommendations from leading substance abuse prevention experts.

Substance abuse among teens is a highly complex behavior. In identifying cough medicine abuse interventions, knowledgeable experts indicate that the best course of action is to address cough medicine abuse prevention, which means addressing the factors that impact the behavior. An examination of published literature points to a number of key factors leading to the prevalence of substance abuse, including

low parental awareness, low perception of risk, low social disapproval, and ready availability.

Since 2003, the industry has been a leader in the efforts to decrease abuse of dextromethorphan. The industry's interventions to-date have already addressed a number of these risk factors with an evidence-based approach, starting with addressing low parental awareness and advocating for educational and legislative vehicles to reduce the availability of dextromethorphan to teens. CHPA's programs have evolved since we began in 2003, and will continue to grow with interventions designed to increase both teens' perceptions of risk about cough medicine abuse and the social disapproval of this type of abuse. These latest interventions, which will launch in 2011, will include a comprehensive digital media program directly targeted at teens to focus the message on the population known to be susceptible to substance abuse.

Overall, the industry's intervention strategies to mitigate dextromethorphan abuse are designed to impact teens' entire environment by targeting the following goals:

- Raise parental, caregiver, and teen-influencer awareness and involvement as to the abuse and its risks;
- Increase the perception of risk among teens by highlighting the risks of abuse;
- Increase social disapproval of the behavior by emphasizing peers' disapproval of abuse and demonstrating that non-abuse is the norm; and
- Reduce dextromethorphan's availability to teens by:
  - Advocating for legislation to establish a national age restriction on purchases of dextromethorphan-containing medicine;
  - Advocating for legislation to prohibit the sale of bulk, unfinished dextromethorphan to parties not registered with FDA; and
  - Encouraging parents and caregivers to engage in monitoring behaviors, such as safeguarding their medicine cabinets, and making sure other parents do likewise.

## **1.5 Recommendations**

CHPA does not believe scheduling of dextromethorphan under the Controlled Substances Act is warranted. This conclusion is based on 50 years of marketing experience and the totality of a review of the data from pharmacology; preclinical and clinical studies related to its abuse liability; a low and flat prevalence of reported abuse from national, government-sponsored surveys; a review of outcomes databases; and dextromethorphan's benefits and risks to public health.

Instead, CHPA recommends:

- Support for expanded educational interventions;
- Calling on Congress to pass legislation for a national age restriction on OTC medicines containing dextromethorphan to prohibit sale to those under age 18;
- Calling on Congress to pass legislation to prohibit the sale of unfinished, bulk dextromethorphan to any party not registered with FDA;
- Calling on Congress to invest in medicine abuse programming;
- Refining questions in the Monitoring the Future study and the Partnership Attitude Tracking Survey to:
  - Better track teen perceptions of risk and social approval of OTC cough medicine abuse;
  - More specifically focus questions to assess dextromethorphan abuse prevalence, in contrast to OTC cough and cold medicines in general, or codeine or promethazine prescription products; and
- Implementing metrics to assess the impact of these plans and to guide on-going and future activities.

The materials in this briefing book reflect the collective work and views of the following CHPA member companies which currently market OTC medicines containing dextromethorphan:

Aaron Industries, Inc.

Bayer HealthCare LLC

Combe Incorporated

McNeil Consumer Healthcare

Merck Consumer Care

Novartis Consumer Health, Inc.

Perrigo Company

Pfizer Consumer Healthcare

The Procter & Gamble Company

Reckitt Benckiser Inc.

## 2. Regulatory Review and Market Data

In the United States, dextromethorphan was first approved for marketing as an antitussive in 1958. It is currently used as an active ingredient in more than 140 cough and cold products that are predominantly available over-the-counter (OTC) (FDA 2008).

In the 1970s, FDA initiated a review process to determine which OTC medicines could be considered "generally recognized as safe and effective" (GRASE). After reviewing all available data in experimentally induced cough, controlled studies in pathologic cough with both subjective and objective efficacy endpoints, and uncontrolled studies in a variety of disease states, FDA published the report of an advisory panel, which deemed dextromethorphan as GRASE in 1976 (FDA 1976). In 1987, the agency issued the Final Monograph for OTC Antitussive Drug Products, confirming that dextromethorphan is a safe and effective (GRASE) cough suppressant (FDA 1987). The marketing of the majority of dextromethorphan-containing products is based on this Final Monograph; newer formulations of dextromethorphan (i.e., extended-release formulations) were approved by FDA under the New Drug Application (NDA) process. The most recent NDA for a new dextromethorphan-containing OTC cough medicine was approved in 2004 (FDA 2004).

Dextromethorphan is also present in a number of prescription-only medicines, at similar dose levels as in OTC products and mainly in combination with the prescription-only first-generation antihistamine promethazine.

Dextromethorphan is the most widely used active ingredient to treat cough. A 2004 survey conducted by the Slone Epidemiology Center showed that in any given week, 1.7% of adult Americans use a dextromethorphan-containing medicine (corresponding to more than 3.5 million adults) (Slone 2004).

Dextromethorphan-containing OTC medicines account for 85 - 90% of all medicines containing a cough suppressant sold in the United States. In the one-year period ending Q1 2010, 36% of American households purchased a dextromethorphan-containing OTC product. Approximately 133 million pack units of dextromethorphan-containing OTC products were purchased during this time period (Nielsen 2010).

Whereas the vast majority of purchases of dextromethorphan-containing OTC products stem from self-medication decisions, there are also purchases of dextromethorphan OTC resulting from doctor prescriptions. According to data from the National Disease and Therapeutic Index (NDTI), there were 3.7 million prescriptions for dextromethorphan OTC products in the one-year period between May 2009 and May 2010. This compares to 5.5 million prescriptions of dextromethorphan prescription-only products in the same period (IMS 2010).

Outside the U.S., dextromethorphan is approved and marketed as a nonprescription cough medicine in numerous countries worldwide which include the vast majority of European countries, Canada, Australia, and Japan (WSMI 2008).

### **3. Need for Access to Over-the-Counter Dextromethorphan**

Dextromethorphan is by far the most commonly used ingredient to treat acute cough. The over-the-counter availability of dextromethorphan meets an important medical, societal and consumer need. This need results from three factors:

- (1) The vast prevalence of acute cough in the American population – the condition for which dextromethorphan OTC is indicated
- (2) The significant health burden this condition poses on individuals and their families
- (3) The importance of allowing OTC access to this safe and effective treatment since there is no substitute available with comparable accessibility, safety profile and/or market experience.

The following sections discuss the important elements and relevant data to be considered in the context of dextromethorphan's availability and legitimate use as an OTC medicine by the American public.

#### **3.1 Prevalence of Cough**

##### **3.1.1 Cough in the General Population**

National survey data show that cough is very prevalent in the general population. It is both the most common symptom for which Americans self-medicate and the most common complaint for which they visit a physician office (NCPIE 2008, Cherry 2008).

Two recent surveys confirmed the high prevalence of cough among American adults. In a nationwide telephone survey conducted in January 2007 by Michaels Opinion Research, 41% of the 3,052 individuals surveyed reported that they experienced a cough in the past three months (Michaels Opinion Research 2007). These findings were consistent with the results of a January 2008 nationwide telephone survey conducted for the National Council on Patient Information and Education (NCPIE). In this study, 43% of the 1,005 individuals surveyed experienced a cough in the previous year. Notably, in the NCPIE survey, cough was more common than allergies (41%), heartburn (31%), severe headache (27%), flu (17%), and rash or hives (8%) (NCPIE 2008).

##### **3.1.2 Cough Associated With the Common Cold**

The common cold, which is recognized as the most common illness in man, is almost always accompanied by an acute cough (Eccles 2005, Irwin 2006). Adult Americans suffer from two to four colds per year. Extrapolation of this incidence

rate to the entire population suggests that people in the U.S. suffer 1 billion colds each year (NIAID 2007). In the 2008 NCPIE survey, 57% of the participating adult individuals reported that they had a cold in the previous year (NPCIE 2008). In another nationwide survey which was conducted in October 2001 (n=2,011), 24% of adults reported that they had experienced a cold in the past four weeks (Bramley 2002).

Several studies have examined the frequency of coughing among individuals with a common cold. In a study of 150 adults with common colds, 94% of participants reported the occurrence of cough during the course of a cold (Barrett 2005). Similarly, in a study of 86 adults, cough occurred in 79 - 83% of individuals during the course of a cold (Curley 1988).

Symptomatic treatment of the common cold has long been established as acceptable medical practice because there is no causal treatment of this viral infection (Rohde 2009). Controlling the symptoms of the common cold with OTC medicines including antitussives is an accepted goal, since symptom relief allows people to carry on with their lives (Eccles 2009).

## **3.2 Health Burden of Cough**

### **3.2.1 Quality of Life Studies**

Health-related quality of life is significantly impaired in individuals with cough. Notably, the degree of health impairment was found to be similar between acute and chronic cough (French 2002). Physical effects of cough include sleep deprivation, hoarse voice, urinary incontinence, syncope, vomiting, chest pains, headache, dizziness, hernia, and lethargy. Adverse social effects include avoidance of social events, interference with work, and interruption of telephone calls. Finally, psychological effects include embarrassment, fear of serious illness, and frustration (Brignall 2008, Irwin 2002).

The numerous physical, social, and psychosocial effects of cough form the domains of two quality of life (QoL) instruments which were developed to provide validated and quantifiable measurements of the health impact of acute and chronic cough: the Cough-specific Quality of Life Questionnaire (CQLQ) and the Leicester Cough Questionnaire (LCQ). Using the CQLQ, French et al found that acute cough, defined as cough of no more than three weeks, adversely affects the quality of life to a similar degree in women and men, i.e., the mean total CQLQ scores did not show gender differences. However, women complained significantly more than men in the domains "wetting the pants" and "exhaustion" and significantly less in the items "concern of cancer" and "having to make lifestyle changes" (French 2005). A study in acute coughers with the LCQ instrument

confirmed the results of the CQLQ trial in that it found a severe impairment of the physical, social, and psychological domains of cough (Yousaf 2009).

The substantial health impact of cough found in these studies is seen as an explanation why OTC cough suppressants are among the most commonly used medicines in the U.S. and also why cough is the single most common reason for medical consultations (French 2005).

### **3.2.2 Cough Interfering With Sleep**

Nighttime sleep disruption due to coughing is a frequently reported complaint and creates a particular burden to individuals. Cough occurring at night not only disturbs the sleep of the sufferer, but also other family members. In addition, in focus group studies, cough sufferers reported that coughing at night has a particularly negative effect on daytime functioning (Vernon 2009).

In a study in 150 individuals with common cold, the incidence rate of sleep disruption due to coughing was 77% (Barrett 2005). In an international population survey of more than 18,000 subjects from 16 countries, including 556 subjects from the U.S., a median of 31% of all participants and 34% of Americans reported that they had “been woken up by an attack of coughing at any time in the last twelve months” (Janson 2001).

In the QoL study by French et al in individuals suffering from acute cough, sleep deprivation and hoarseness were found to be the two highest ranked physical symptoms having an adverse impact on people’s lives (French 2005). These results were confirmed through the study by Barrett and colleagues, in which common cold sufferers rated “cough interfering with sleep” as more bothersome than the majority of other cold-related symptoms such as headache, body ache, and plugged or runny nose. Only the common cold items “feeling run down” and “lack of energy” ranked higher than sleep disruption caused by coughing (Barrett 2005).

### **3.2.3 Cough and Urinary Incontinence**

Urinary incontinence is another frequently occurring negative effect of cough which poses a significant physical and psychological burden in particular to women older than 45 years of age. This condition is caused by the cough-induced abrupt and more than 5-fold increase of the intravesical pressure - from approximately 20 cm H<sub>2</sub>O at rest to more than 100 cm H<sub>2</sub>O with maximum cough - exceeding the urethral closure pressure in incontinent women (DeLancey 2010).

Urinary incontinence has been observed to affect between 17 and 55% of adult women. In a Canadian study it was found that women  $\geq 45$  years of age who reported “usually having a cough” were significantly more likely to be incontinent. Fifty percent (50%) of women with stress urinary incontinence reported that they experience urine loss when they cough. Only 40% of incontinent women indicated they had discussed urine loss with their physician (Swanson 2005).

### **3.2.4 Role of Cough in Transmission of Airborne Pathogens**

In addition to the health burden of coughing on an individual’s life, cough also impacts certain infectious diseases at the population level. Namely, it is an important factor in the spread of airborne viruses. According to the Center for Disease Control and Prevention, coughs and sneezes are the main route that influenza viruses are spread from person to person (CDC 2010). Aerosol dissemination via coughing, sneezing, talking and even breathing was shown to be the transmission route of chickenpox, measles, and varicella-zoster virus as well (Tang 2009a). While hand contact is seen as an important alternative transmission route for common cold viruses, these germs are also transferred from person to person through dissemination of drops of mucus (NIAID 2007, Hendley 1988).

Several studies have examined the aerodynamic characteristics of coughing. When one coughs, approximately two liters of air is expelled (Tang 2009a). The air released travels at a speed as fast as  $13 \text{ m s}^{-1}$  (Tang 2009a) and over a distance of approximately three to six feet from the mouth (CDC 2010, Tang 2009b). A single cough can generate about 3000 droplets, the same number as talking for five minutes (Tang 2006). On the basis of the number and size of expelled droplets it was estimated that around 20,000 influenza viruses can be expelled in one cough (Tang 2010).

### **3.3 Economic Burden of Cough**

Since acute cough is predominantly associated with the common cold which manifests itself in a range of symptoms, there is no literature on the economic impact of acute cough alone. We believe, however, that the available data on the common cold can be considered as a valid reference since almost all colds are accompanied by cough. Additionally, many cold sufferers perceive coughing as the most burdensome cold symptom. Therefore, it can be assumed that the contribution of cough to the economic burden of the common cold is significant.

The economic impact of the common cold is substantial because of its vast prevalence in the population and the significant health burden it imposes on individuals. This is reflected in the results of research which shows that the common cold leads to a significant loss of work and school days (absenteeism) as well as a marked productivity loss while people are working (presenteeism).

To assess the work productivity impact of the common cold, Bramley et al conducted a telephone survey of 2,011 adult individuals during the peak cold season of 2001. The mean duration of a cold was 6.4 days. It was found that employed cold sufferers lost an average of 8.7 work hours per cold episode (2.8 absenteeism hours; 5.9 hours of on-the-job productivity loss). The total time missed resulted both from work absenteeism (due to doctor visits, arriving late at work, staying home from work or leaving early) and productivity losses while at work. On the basis of these survey results, the authors estimated 69 million lost workday equivalents attributable to absenteeism and 145 million lost work day equivalents attributable to on-the-job productivity loss. These estimates translated into an economic cost of lost work productivity due to the common cold of \$25 billion per year (Bramley 2002).

The findings of Bramley et al are consistent with those of a subsequent publication by Fendrick et al. The latter study was based on a telephone survey of 4,051 American households conducted between 2000 and 2001. Based on their findings, the authors estimated that 70 million work days attributable to employee absenteeism are missed each year due to the common cold. This estimate translated into a cost of work absenteeism due to colds of \$8 billion per year. In addition to work absenteeism because of employees experiencing a cold themselves, the study estimated that 126 million workdays annually are missed by parents caring for children who suffer from a cold (translating into a cost of work absenteeism of \$14.6 billion per year) (Fendrick 2003).

### **3.4 Self-care and Health Care System Utilization for Cough**

#### **3.4.1 Self-Care**

As discussed in more detail below, several studies have demonstrated that the majority of Americans self-medicate for cough and the symptoms of a common cold. Self-medication of cough with an OTC medication is the predominant action taken to treat cough, and survey participants reported that the main reason for their self-care decision is familiarity with the condition and its management from previous experience (NCPIE 2008).

In a 2007 nationwide survey of 3,052 adult Americans, 1,233 participants reported that they had experienced a cough due to a common cold or another respiratory condition in the past three months. Sixty-six percent (66%) of these individuals reported that they self-medicated their cough with an OTC medication, 39% consulted a physician, 26% used a prescription medication, and 18% did not seek treatment for their cough. The response categories were not mutually exclusive as the total percentages add up to 149%. This indicates that a number of survey

participants who used an OTC cough medicine also consulted a doctor (Michaels Opinion Research 2007).

The findings of the survey from 2007 are supported by the results of two other studies.

In a 2008 nationwide survey, the common cold and cough were the most common conditions for which the 1,005 adults surveyed self-medicated with an OTC medicine. Fifty-six percent (56%) of individuals with a common cold reported that they typically treat this condition with an OTC medicine. Among the 650 individuals who indicated that they typically self-medicate with OTC medications, 90% reported that they do so because they are familiar with how to treat their illness from past experience. Other reasons these respondents cited for self-medicating were illness not serious enough to warrant a doctor visit (78%), save a trip to the doctor's office (78%), save time (77%), and save money (70%) (NCPIE 2008).

Another large nationwide telephone survey was conducted between 2000 and 2001. In this survey of 4,051 adults, more than two-thirds (69%) of survey respondents reported that they self-medicate with an OTC product when they have symptomatic common cold episodes. In contrast, only 16% of individuals indicated that they seek medical attention at a physician's office for the same condition (Fendrick 2003).

### **3.4.2 Healthcare System Utilization**

While the majority of cough and cold sufferers self-medicate with an OTC medicine, cough is also the leading cause of doctor visits in the United States. The available data indicate that individuals consult their physician primarily for chronic cough and when they perceive their cough as abnormally severe but rarely when they have an uncomplicated cough due to the common cold.

Cornford conducted a comparison of the illness behaviors between adult individuals with cough who consulted a physician (n=30) and those who had cough but did not consult a physician (n=26). The study found that subjects who did not consult a physician considered their cough as "normal" and rarely as severe or as interfering with social roles. In contrast, individuals who did consult a physician believed that their cough was "abnormal" (usually abnormally severe) and almost half felt that their cough interfered with social roles. Furthermore, the "physician consulting" group differed from the "nonconsulting" group in that they often believed antibiotics were necessary for their particular cough (Cornford 1998).

The findings of the study by Cornford are consistent with National Ambulatory Medical Care Survey (NAMCS) data which indicate that cough associated with underlying conditions of severe and/or chronic nature is the main reason for physician visits. In an analysis of NAMCS data from 1980 to 1994 that focused on office visits in which the chief complaint was cough, the leading primary diagnosis was bronchitis (41.7% of cough-related physician visits), followed by upper respiratory tract infections (15.9%), asthma (5.7%), rhinosinusitis (5.6%), pneumonia (4.7%), influenza (2.6%), pharyngitis (2.0%), and nasopharyngitis/common cold (1.5%) (Metlay 1998).

In the most recently reported NAMCS study, cough was the most frequently mentioned illness or injury reason for a physician office visit. Cough accounted for more than 26 million physician-office visits in 2006. No information was provided in this survey on the underlying diagnosis, severity and nature of cough (Cherry 2008).

### **3.5 Public Health Benefits of Over-the-Counter Availability of Dextromethorphan**

Dextromethorphan OTC provides millions of American consumers with a cost-effective and safe treatment option for acute cough episodes. The accessibility of dextromethorphan OTC allows individuals and family caregivers to quickly and effectively counter the negative impact of cough on their own and their family's life, thereby enabling them to continue with their work and private duties.

As discussed in Section 2, dextromethorphan is the most widely used OTC cough suppressant. Apart from dextromethorphan, there are only three other ingredients for oral ingestion which were determined by FDA as safe and effective for the use in OTC medicines indicated for temporary cough suppression: low dose codeine, diphenhydramine, and chlorthalidone. None of these three can be considered a substitute for dextromethorphan OTC because of differences in access, market experience and safety profile: **codeine** is a scheduled controlled substance and, therefore, only available with a prescription in at least 18 states; there is limited marketing experience with **chlorthalidone** in the U.S. (chlorthalidone has a pharmacological profile comparable to dextromethorphan; Boyd 1960); and the first-generation antihistamine **diphenhydramine** can cause drowsiness.

As summarized below, the public health benefits of dextromethorphan OTC can be described on three levels: an individual, a population, and a societal level.

### **3.5.1 OTC Benefits on Individual Level**

On the individual level, the benefits of dextromethorphan OTC are grounded in its access. Unlike prescription-only medicines which can only be purchased at pharmacies, OTC cough medicines are available at various types of outlets including corner stores and supermarkets. There are approximately 54,000 pharmacies in the U.S. compared to an overall 750,000 retail outlets (including pharmacies) which can sell OTC products. Consequently, the odds are high that consumers can buy an OTC medicine at a retail outlet that is closer than the nearest pharmacy (GAO 1995).

Due to the availability of dextromethorphan without prescription, consumers save time and costs. The time element of access is an important benefit OTC medicines offer to individuals. In a 2008 study in 1,005 individuals, 77% of participants reported that they self-medicate with OTC medicines because it saves them time (NCPIE 2008). The time-savings accrued from OTC medicines result primarily from the time saved for a doctor visit to get a prescription. A scheduled doctor office visit requires on average two to four hours, including time spent traveling and time spent at the doctor's office (Pisu 2005, Prosser 2008).

The cost savings element of OTC availability includes foregone out-of-pocket costs for doctor visits and prescriptions, the costs of transportation, the costs of time spent travelling and waiting at a doctor's office.

Because a physician visit usually means time out of work, OTC availability prevents self-employed workers and hourly employees from losing wages. In fact, individuals in a variety of employment situations are not always able to get time away from work during normal business hours to receive medical services.

In addition to time and cost savings, the current OTC marketplace offers the benefit of choices of dextromethorphan medicines in terms of pack sizes, product forms, and price ranges.

### **3.5.2 OTC Benefits on Population and Societal Level**

On the population level, the OTC availability of dextromethorphan reduces employee absenteeism since individuals don't have to miss work to obtain a prescription for a cough medicine. In addition, OTC access to dextromethorphan can help to maintain employee productivity. It has been demonstrated that on-the-job productivity is significantly diminished when people suffer from cough and cold conditions (Bramley 2002).

On the societal level, the healthcare system benefits from the OTC availability of dextromethorphan due to the reduction of unnecessary use of healthcare services. These services include consultations by primary care physicians, nurse practitioners, community clinics, and urgent care centers which are the first contact

for most people looking to receive treatment for cough and cold symptoms. Furthermore, dextromethorphan OTC saves health plan spendings on provider reimbursement and prescription medicines.

### **3.6 Potential Consequences of Scheduling Dextromethorphan**

Scheduling dextromethorphan under the Controlled Substances Act would impose significant barriers to convenient access for those seeking relief for cough. Depending on the schedule, these barriers range from requiring a physician visit to obtain a prescription for medicines with the ingredient, to requiring a prescription in at least 18 states and severely restricting the number of outlets which may distribute the medicine in all other states through pharmacist-only dispensing and record-keeping requirements.

Depriving consumers of the option to self-medicate with dextromethorphan would have substantial public health consequences because (1) cough is the most prevalent medical condition in the American population, and (2) cough poses a significant health burden on individuals who would likely seek alternative treatments if dextromethorphan ceased to be available in over-the-counter medicines.

Consumers are likely to react in one of three ways:

- (a) Consult a physician to obtain a prescription medicine
- (b) Choose another OTC treatment for cough (such as diphenhydramine)
- (c) Leave cough untreated

#### **(a) Consult a physician to obtain a prescription medicine**

While currently individuals suffering from cough and the common cold rarely visit a physician office, the removal of dextromethorphan's OTC availability would potentially result in an increased number of doctor office visits for acute cough and cold conditions. This would result in a loss of valuable healthcare resources (especially in the primary care area) resulting from increased administrative burdens for scheduling visits, conducting consultations, and handling additional prescriptions. Additionally, a rise of physician visits for cough and cold symptoms would likely be accompanied not only by an increase of prescriptions for prescription-only cough suppressants, but also by a further increase of an already unacceptably high number of inappropriate antibiotic prescriptions. Studies have consistently shown that when people consult a physician for viral respiratory infections, antibiotics are frequently prescribed (AHRQ 2006). For example, in a retrospective analysis of physician records of almost 40,000 episodes of viral

upper respiratory tract infections in adults, in nearly half (48%) of all doctor visits antibiotics were prescribed (Hueston 1999).

**(b) Choose another OTC treatment for cough**

If dextromethorphan were not available over-the-counter, this would likely lead to an increased use of other OTC cough ingredients such as diphenhydramine and chlorpheniramine. Diphenhydramine cannot be considered a comparable substitute for dextromethorphan because it causes drowsiness, and chlorpheniramine is a substance with little market experience in the United States (chlorpheniramine has a pharmacological profile comparable to dextromethorphan).

**(c) Leave cough untreated**

As large surveys have shown, currently the vast majority (more than two thirds) of Americans treat their cough with OTC medicines. If individuals choose to stay untreated because dextromethorphan OTC was not available, they would have to endure a reduced quality of life and a negative impact on their work and private activities. From a societal point of view, this would probably increase the number of missed work days and a decrease in work productivity.

The move of pseudoephedrine-containing cold and allergy medicines from nonprescription to prescription-only status in the state of Oregon in 2006 can be seen as a reference in terms of the impact of such a change on product use. The estimated monthly distribution of all pseudoephedrine-containing cold medicines dropped from a level of approximately 150,000 to 200,000 units sold between July 2005 and June 2006 to steady monthly levels of approximately 10,000 units sold in the 24 months after the switch became effective in July 2006 (Avalere 2009). It can be hypothesized that this drop by more than 90% reflects that people used other medicines to manage their cold and allergy symptoms. Alternatively, some Oregon residents may have purchased pseudoephedrine-containing products in near-by states without a prescription requirement. Some may have decided to stay untreated. Applying this scenario to a move of dextromethorphan to prescription-only status, one can predict that nationwide millions of current dextromethorphan OTC users would treat their cough either with other OTC ingredients (such as diphenhydramine) or with prescription-only ingredients (including codeine and benzonatate).

### **3.7 Conclusion**

Scheduling dextromethorphan under the Controlled Substances Act would restrict its legitimate medical use as a self-treatment for cough. Depriving consumers from the option to self-medicate with dextromethorphan would probably have substantial public health consequences in terms of an increased utilization of healthcare system resources for acute cough and cold conditions and an increased use of non-equivalent alternative treatments.

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## 4. Analysis of Abuse Potential

### 4.1 Summary of Evaluation: Scheduling Not Recommended

CHPA has consulted with leading experts in substance abuse, abuse liability assessment, and controlled substance scheduling determination to evaluate relevant data concerning dextromethorphan. These experts do not recommend Controlled Substance Act scheduling. CHPA does not believe scheduling of dextromethorphan is warranted. This conclusion is based on the totality of a review of the data from pharmacology; preclinical and clinical studies related to its abuse liability; the prevalence of reported abuse from national, government-sponsored surveys; a review of outcomes databases; and dextromethorphan's benefits and risks to public health. There are more targeted, more effective, and less disruptive interventions to address dextromethorphan abuse. CHPA took into account methods described in the 8-factor analysis under the Controlled Substances Act and FDA's Guidance for Assessment of Abuse Potential of Drugs.

The following sections review pharmacology (Section 4.1.1), abuse potential studies (Section 4.1.2), information on patterns of reported abuse as seen through national surveys (Section 4.1.3), the significance of abuse as reviewed in outcomes-related databases (Section 4.1.4), and the benefits and risks to public health (Section 4.1.5). Taken together, this analysis supports the recommendation against scheduling.

**Pharmacology:** Dextromethorphan is a cough suppressant which has a central action on the cough center in the medulla. It is believed to suppress cough by altering the threshold signal to cough initiation in the central nervous system.

Dextromethorphan is the d-isomer of levomethorphan. Although structurally similar to other morphine derivatives, dextromethorphan is a non-narcotic cough suppressant. It does not act as an opioid receptor agonist, and it is devoid of morphine-like effects.

**Abuse potential studies:** Clinical studies find that, at high doses (e.g., 8-20 times the maximum OTC dose), dextromethorphan can exert mixed clinical effects, eliciting both euphoria and dysphoria. These effects are often associated with nausea and vomiting, as well as "disliking" sensations in abuse liability evaluations. Dysphoria and "disliking" increase dose-dependently. These effects do not suggest potential for chronic abuse.

Withdrawal or tolerance do not appear to be factors in misuse and abuse of dextromethorphan. There are no controlled pre-clinical or clinical studies demonstrating that dextromethorphan produces physical dependence as measured by tolerance or withdrawal, however, there are isolated case report suggesting it may produce psychological dependence.

These clinical findings are consistent with qualitative research among substance abusers which shows little recurring abuse of dextromethorphan. Users describe the experience as unsatisfactory as a result of negative effects, including dysphoria, nausea, blurred vision, and disorientation.

**Prevalence of reported abuse:** National surveys show the abuse of OTC cough medicines, many of which contain dextromethorphan, is limited in its prevalence and scope, with reported abuse concentrated in teens and, to a lesser degree, young adults. Prevalence is flat over the four years for which national data is available.

**Outcomes databases:** Databases which examine outcomes, including substance abuse treatment admissions or emergency room visits for non-medical use, reflect measurable but comparatively low levels of negative health outcomes from reported abuse. These databases also provide further support to the finding that teens and young adults who abuse OTC cough products appear to discontinue such abuse in adulthood.

**Risk and benefit to public health:** Dextromethorphan has a long history of use, and is well-tolerated when used as directed. Intentional abuse has been reported over time; however, the incidence of such abuse is low, particularly given its long history of widespread use. In general, health consequences of dextromethorphan abuse appear infrequent and not serious, but can lead to morbidity, emergency room visits, and, in very rare instances, death.

The scheduling of dextromethorphan under the Controlled Substances Act would itself have a large *negative* public health impact by limiting access for those who have a need to treat their cough. OTC access provides a public health benefit by allowing self-treatment of acute cough, saving doctor visits and prescription costs.

#### **4.1.1 Pharmacology**

##### **4.1.1.1 Chemistry and Molecular Pharmacology**

Dextromethorphan (d-3-methoxy-N-methyl-morphinan) is the dextro isomer of levomethorphan, a semisynthetic morphine derivative. Dextromethorphan is mostly used in the form of its monohydrated hydrobromide salt, a practically odorless, white crystalline powder with a bitter taste.

Dextromethorphan is a centrally acting cough suppressant. It is believed to suppress cough by altering the threshold for cough initiation through effects in the medulla oblongata. While its pharmacology is incompletely understood, dextromethorphan has been shown to bind to receptors implicated in the cough

response, including the sigma-1 receptors and N-methyl-D-aspartate (NMDA) receptors.

Although structurally similar to other morphine derivatives, dextromethorphan is classified as non-narcotic cough suppressant (FDA 2009). Dextromethorphan does not act as an opioid receptor agonist, and it is devoid of morphine-like effects (USDOJ/DEA 2010, Jasinski 2000).

#### **4.1.1.2 Antitussive action**

Dextromethorphan is a cough suppressant which has a central action on the cough center in the medulla. As mentioned in Section 4.1.1.1, it is believed to suppress cough by altering the threshold signal to cough initiation in the central nervous system (CNS) (Canning 2009).

Dextromethorphan has been demonstrated to suppress cough in various animal models as well as in human studies with experimentally induced and natural cough (Canning 2009, Fuller 1989, Grattan 1995, Ramsey 2007, Pavesi 2001). Both in animals and human studies, a dose-response relationship for dextromethorphan's antitussive effect was shown in that increasing doses produced increasing levels of cough suppression (Fossati 1995, Bolser 1999, Kotzer 2000, Aylward 1984).

#### **4.1.1.3 Other Pharmacological Effects (Including Psychoactive Effects)**

At doses used for cough suppression, dextromethorphan has no effect on respiration, the cardiovascular system, the gastrointestinal tract, and the mucociliary activity. Also, it has little or no sedative and analgesic action (FDA 1976, Karttunen 1990, Bem 1992, Siu 2007). In a study in healthy volunteers, it was shown that dextromethorphan 60 mg p.o. does not enhance the respiratory depressant effect of a single dose of 60 mg morphine p.o. (Jasinski 2000).

The CNS pharmacology of dextromethorphan at doses  $\geq 10$  times greater than the maximum therapeutic dose was described as comparable to that of other substances that antagonize NMDA receptors (e.g., phencyclidine and ketamine). *Table 1* below provides a tabulation of dextromethorphan doses and their reported behavioral effects. The maximum therapeutic dose of dextromethorphan to treat cough is 30 mg, corresponding to 0.43 mg/kg for an individual with a body weight of 70 kg. The psychoactive effects are observed at doses far exceeding the therapeutic doses.

**Table 1. Dextromethorphan Doses and Behavioral Effects**

<b>Plateau</b>	<b>Dose</b>	<b>Behavioral Effects</b>	<b>Dose Multiple vs Maximum Therapeutic Dose</b> (30 mg corr. to 0.43 mg/kg in a 70 kg individual)
1 <sup>st</sup>	100-200 mg (1.4 – 2.8 mg/kg in a 70 kg individual)	Mild stimulation	3.3 – 6.7 x
2 <sup>nd</sup>	200-400 (2.8 – 5.6 mg/kg)	Euphoria and hallucinations	6.7 – 13 x
3 <sup>rd</sup>	300-600 (4.3 – 8.6 mg/kg)	Distorted visual perceptions Loss of motor coordination	10 – 20 x
4 <sup>th</sup>	500-1500 (7.1 – 21.4 mg/kg)	Dissociative sedation	16.7 – 50 x

From USDOJ/DEA 2010

Importantly, high doses of dextromethorphan that make individuals feel drunk or high, also frequently give them dysphoria, nausea, and vomiting. Findings from a clinical study demonstrated that orally administered dextromethorphan 2 - 4.5 mg/kg dose-dependently increased ratings on the Addiction Research Center Inventory (ARCI) LSD Dysphoria and the Cole/ARCI Unpleasantness scales (Zawertailo 2010). ARCI scales are explained in more detail in Section 4.1.2.2.

At high doses ( $\geq 2.2$  mg/kg), adrenergic effects (e.g., hypertension, tachycardia, and diaphoresis) were observed in individual cases and also attributed to dextromethorphan's NMDA receptor antagonism (Chyka 2007).

#### **4.1.1.4 Pharmacokinetics and Metabolism**

Dextromethorphan, like many other commonly used medications, is a substrate of the polymorphic cytochrome P450 enzyme 2D6 (CYP2D6) (Evans 1993). The main metabolite of dextromethorphan is dextrorphan, which is produced via O-demethylation. This reaction is catalyzed by CYP2D6 (Schadel 1995). The vast majority of the population (>90%) excretes at least three times more dextrorphan than dextromethorphan in the urine and is classified as extensive metabolizers (EMs). The remainder of the population, less than 10%, excretes a higher amount of the parent compound, dextromethorphan, compared to dextrorphan; this group is classified as poor metabolizers (PMs) (Vetticaden 1989). Poor metabolizers have a gene deletion or gene mutations that results in the absence of CYP2D6 (Capon 1996).

The incidence of the CYP2D6 PM phenotype varies among ethnic groups. The incidence of the CYP2D6 PM phenotype is approximately 5 - 10% in Caucasians

and Mexican Americans (Evans 1993, Casner 2005), 2 - 6% in African Americans (Evans 1993, He 1999), 1.6% in the Indian population (Buch 2001), and 1% or lower in Japanese and Chinese populations (Nagai 1996, Cai 1997).

Dextromethorphan is well absorbed from the gastrointestinal tract with maximum dextromethorphan plasma concentrations occurring approximately 1 to 4 hours after oral administration in EMs and 4 to 8 hours after oral administration in PMs. Dextromethorphan has a plasma elimination half-life of approximately 1 to 4 hours in EMs and 17 to 42 hours in PM subjects. The plasma elimination half-life of the main metabolite dextrorphan is approximately 1 to 3 hours in EMs and 5 to 13 hours in PMs (Silvasti 1987, Schadel 1995, Capon 1996).

In addition to the main metabolic pathway for dextromethorphan, O-demethylation catalyzed by CYP2D6 resulting in dextrorphan, there is also a minor metabolic pathway. In this minor pathway, dextromethorphan is metabolized to 3-methoxymorphinan through N-methylation catalyzed by CYP3A4/5. Both dextrorphan and 3-methoxymorphinan may be further metabolized to 3-hydroxymorphinan, and dextrorphan and 3-hydroxymorphinan undergo conjugation. Dextromethorphan and its metabolites are excreted via the kidney (Takashima 2005, Veticaden 1989, Schadel 1995).

No chiral conversion of dextromethorphan to the opioid levomethorphan occurs in humans (Bem 1992).

#### **4.1.2 Abuse Potential Studies**

##### **4.1.2.1 Animal Studies**

Dextromethorphan's abuse potential was tested in two types of animal models, drug discrimination studies and self-administration studies.

##### **Drug discrimination studies**

Drug discrimination models determine whether the test drug produces an effect in animals similar to effects produced by a known drug of abuse. Animals (typically rats or monkeys) are trained to press one bar when they are dosed with a drug of abuse and a second bar when dosed with placebo. A challenge session with the test drug determines which of the two bars the animal presses more often, as an indicator of whether the test drug is recognized or perceived by the animal as the known drug of abuse, i.e., whether the test drug *substitutes* for the drug of abuse (FDA 2010).

Results with phencyclidine (PCP) trained animals were mixed, showing both a dose dependent substitution (Nicholson 1999, Holtzman 1982) and a lack of

substitution (Mori 2001, Holtzman 1994). In animals trained with ketamine, dextromethorphan showed substitution (Narita 2001), but it failed to substitute for tetrahydrocannabinol (Barrett 1995), nicotine (Zakharova 2005, Wright 2006), pentobarbital (Winger 1982), dizocilpine (France 1991), 2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid (Bobelis 1993), profadol, naltrexone, ethoheptazine codeine, and morphine (Overton 1979).

Conversely, when animals are trained with dextromethorphan, the potential for substitution depends on the drug of abuse. Dizocilpine and cyclazocine substituted for dextromethorphan, whereas morphine did not (Gavend 1995).

### **Self-administration studies**

Self administration assays assess the rewarding properties of drugs in animals (FDA 2010). In self-administration studies, it was found that dextromethorphan is self-administered by Rhesus monkeys initially trained to self-administer PCP (Nicholson 1999). In contrast, dextromethorphan was not self-administered by naïve rats (rats with no history of exposure to other drugs) which were trained to self-administer intravenously dextromethorphan in combination with diphenhydramine (Jun 2004).

#### **4.1.2.2 Human Studies**

Abuse potential of dextromethorphan has been assessed in several clinical studies using well-recognized research methodologies. High dextromethorphan doses (oral doses at least 6 times the maximum therapeutic dose) were found to be associated with psychoactive effects such as euphoria but also substantial dysphoria. The mixed clinical effects of dextromethorphan at high doses in eliciting both euphoria and dysphoria likely contribute to limiting the appeal of its use as a drug of choice for abuse.

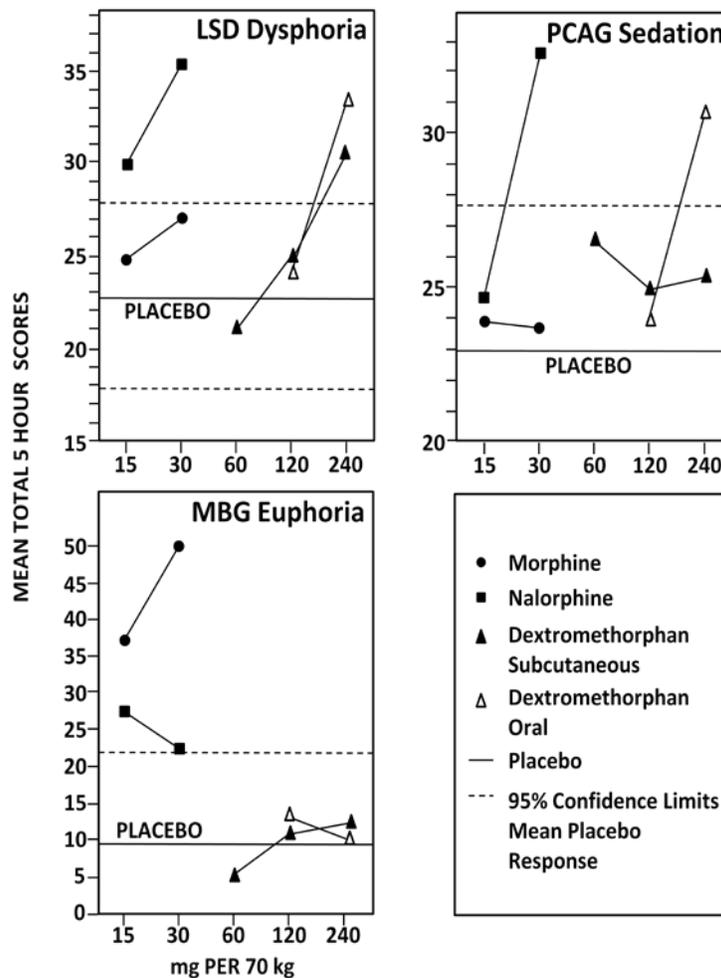
### **The Addiction Research Center Inventory (ARCI) studies**

The Addiction Research Center Inventory (ARCI) is a questionnaire with empirically derived scales developed to distinguish a given drug from placebo or to discriminate between drugs or drug groups. Five scales are of particular interest: MBG / morphine-benzedrine group scale, as an index of euphoria; LSD / lysergic acid diethylamide specific scale as an index of dysphoria and somatic symptoms; PCAG / pentobarbital-chlorpromazine-alcohol group scale as an index of sedation; A / amphetamine and BG / benzedrine group scales are both indices of amphetamine-like effects (Griffiths 2003).

In a placebo-controlled study published in 1971, ten volunteers were given dextromethorphan 120 and 240 mg/70kg orally and in s.c. doses of 60, 120 and 240 mg/70kg. These dosages were compared in the same subjects to nalorphine

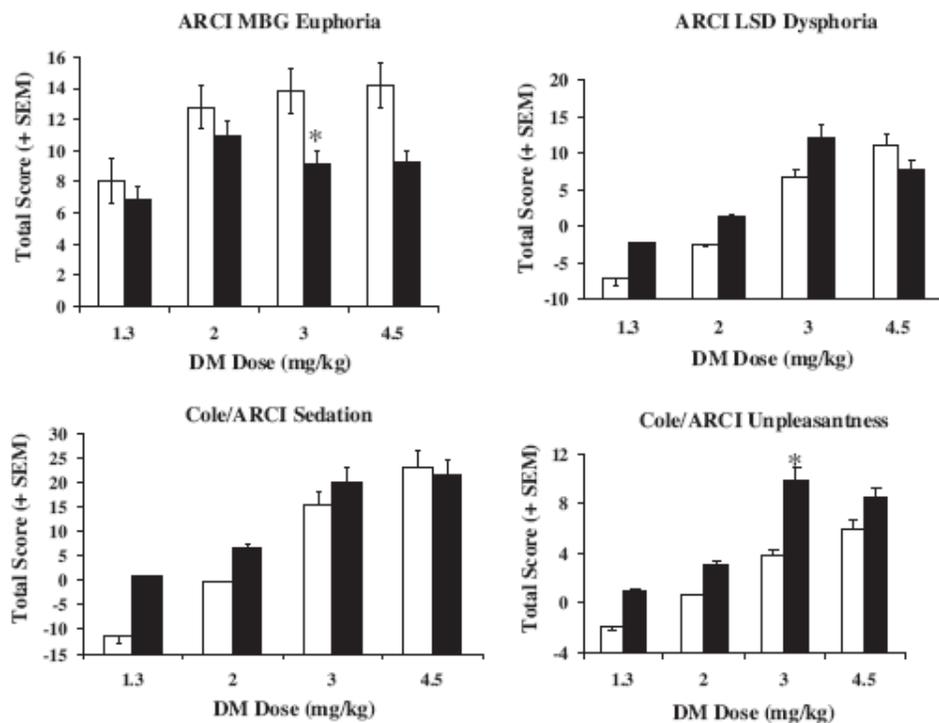
and morphine which were given subcutaneously in doses of 15 and 30 mg/70kg. The results showed that the responses to dextromethorphan were substantially different to those with morphine. Similar to nalorphine, dextromethorphan 240 mg/70kg orally (corresponding to 8 times the maximum therapeutic dose) and s.c. produced higher scores than morphine on the LSD scale indicative of marked dysphoria (see *Figure 1*). On the PCAG sedation scale, only the higher oral dextromethorphan dose 240 mg/70kg was associated with marked elevations. Notably, dextromethorphan produced neither opiate-like symptoms nor significant “liking” scores on the MBG scale (Jasinski 1971).

**Figure 1.** Dose response curves for orally and subcutaneously administered dextromethorphan, subcutaneously administered morphine, subcutaneously administered nalorphine and placebo on the LSD items, the PCAG items, and morphine benzedrine group (MBG) items from the subjective drug effect questionnaire (Jasinski 1971) (scale descriptors added).



The earlier findings reported by Jasinski et al were confirmed in a recent study in eight male healthy volunteers in which oral dextromethorphan doses between 1.3 mg/kg and 4.5 mg/kg produced parallel dose-dependent increases on the MBG euphoria scale and the LSD dysphoria scale (see *Figure 2* below). In an individual crossover, each individual ingested dextromethorphan with and without pre-treatment with quinidine, a substance that blocks the activity of CYP2D6 thereby mimicking poor metabolizer status. As shown in *Figure 2*, poor metabolizer status was associated with increased ratings for dysphoria, sedation, and unpleasant feelings, and decreased ratings for euphoria. These results indicate that the parent drug dextromethorphan produces more unpleasant reactions and less euphoric effects than its main metabolite dextropropriphan. Therefore, the authors of the study suggested that the abuse liability of dextromethorphan would be lower in poor metabolizers (Zawertailo 2010).

**Figure 2.** Dextromethorphan dose-response plots for the ARCI scales of subjective drug effects either with (filled bars) or without pretreatment (open bars) with 100 mg oral quinidine (Zawertailo 2010).



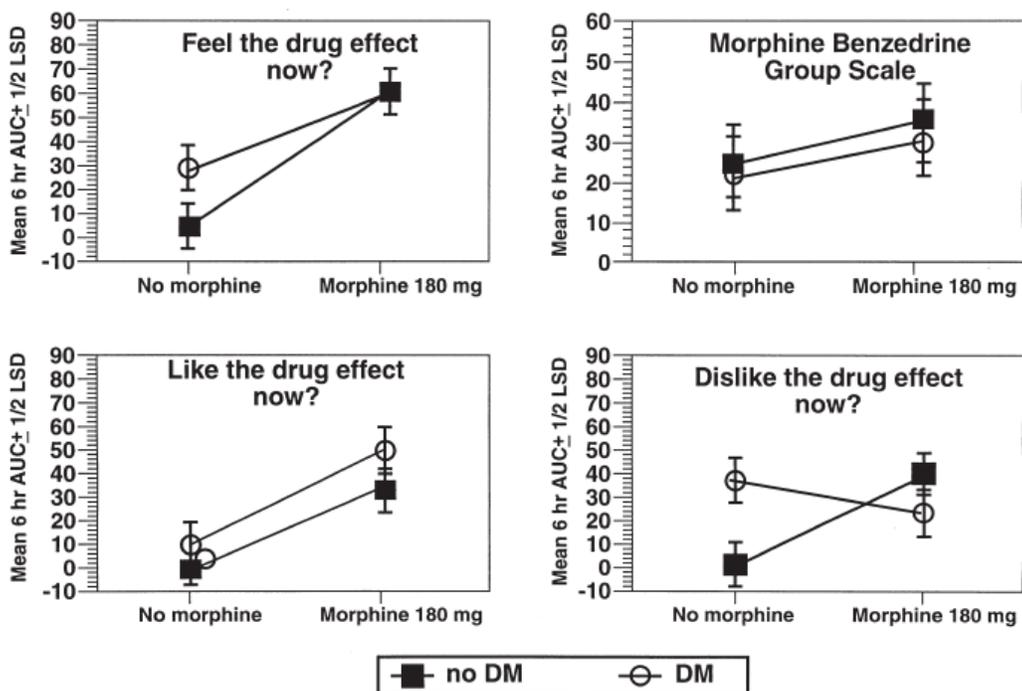
filled bars = poor metabolizer status

open bars = extensive metabolizer status

Similar results were found in a study in 20 opiate users. As expected, a single dose of 180 mg morphine p.o. was associated with increases on the MBG euphoria scale and on a drug “liking” scale (see *Figure 3*). Dextromethorphan 180

mg p.o. (corresponding to 6 times the maximum therapeutic dose) produced no morphine-like effects and did not potentiate any of the effects of morphine. In addition, dextromethorphan alone elevated scores on a “dislike” scale, this effect was reduced when morphine was given at the same time. It was concluded that dextromethorphan at these doses neither caused nor enhanced euphorogenic effects in opiate users (Jasinski 2000).

**Figure 3.** Effect of dextromethorphan 180 mg p.o. on the morphine response in opiate users (Jasinski 2000).



### Neuropharmacological challenge studies in alcohol-dependent individuals

Soyka et al conducted a placebo-controlled study in 20 recently detoxified alcohol-dependent individuals and ten healthy volunteers who served as a control. In both groups, an oral dose of 2 mg/kg dextromethorphan (this corresponds to approximately 5 times the maximum therapeutic dose) produced ethanol-like effects on the Alcohol Sensation Scale (AST)(Soyka 2000). These findings are consistent with observations by drug abusers who report mild drunkenness at doses between 1.5 and 2.5 mg/kg (Cone 2006).

## **Behavioral and cognitive performance tests**

In a study in eight male healthy volunteers, dextromethorphan doses between 1.3 mg/kg and 4.5 mg/kg were associated with dose-dependent decreases in the digit symbol substitution test (DSST; a measure of cognitive performance and speed) and the manual tracking test (an instrument shown to be sensitive to psychomotor impairing effects) (Zawerteilo 2010). These findings of an impaired cognitive and psychomotor performance are also consistent with observations by drug abusers who report sensations of drunkenness at doses between 1.5 and 2.5 mg/kg (Cone 2006).

In sum, the results of human abuse liability studies do not characterize dextromethorphan as a substance with a high potential for abuse in the general population.

### **4.1.2.3 Physiological Dependence Liability**

Withdrawal or tolerance do not appear to be factors in misuse and abuse of dextromethorphan.

Review of the literature did not identify any pre-clinical or clinical studies of dextromethorphan withdrawal or tolerance. In humans, case reports suggest dextromethorphan does not produce physical dependence, but can produce psychological dependence (ie, repetitive or compulsive behavior apart from evidence of withdrawal or tolerance). Tolerance has also been noted in case reports (Cranston and Yoast 1999, CESAR 2007, Schwartz 2005, White 1995, Miller 2005). Taken together with the discussion on mixed clinical effects of both euphoria and dysphoria, this suggests a low dependence potential.

### **4.1.3 Patterns of Reported Abuse**

Since dextromethorphan has been widely used over the last 50 years, there is extensive experience with this ingredient. Observations of isolated reports of dextromethorphan abuse have been made since its first marketing; however, reported abuse has historically been concentrated most highly among teens and young adults (FDA panel report 1976, AMA 2004). Since 2006, national drug abuse surveys have included questions on OTC cough and cold medicines. The first of these surveys is the National Survey on Drug Use and Health (NSDUH), in which less than 0.6% of respondents ages 12 and older report past year use of OTC cough and cold medicines “to get high.” The second of these surveys is Monitoring the Future (MTF), which looks at 8<sup>th</sup>, 10<sup>th</sup>, and 12<sup>th</sup> graders. Approximately 5% of Monitoring the Future respondents report past year use of OTC cough medicine “to get high”, with approximately half reporting use one or two times. It should be noted that neither NSDUH nor MTF ask past year use

questions specific to dextromethorphan. Rather, the questions go to the larger category of OTC cough and cold medicines.

Together, data from these surveys demonstrate that while there is abuse or attempts to abuse OTC cough and cold medicine, the overall prevalence of abuse is comparatively low contrasted with other substances. Abuse appears to be concentrated among teens and young adults, particularly those with histories of alcohol, marijuana and/or tobacco use. Nonmedical use and abuse outside of these populations appears to be rare.

A third means to illustrate a low overall prevalence of abuse is through law enforcement reports. The National Forensic Laboratory Information System (NFLIS) collects solid dosage drug analyses results from state and local forensic laboratories. Dextromethorphan was identified in under 0.01% of exhibits in the first six months of 2008.

#### **4.1.3.1 National Survey on Drug Use and Health**

The National Survey on Drug Use and Health (NSDUH) is administered by the Office of Applied Studies of the Substance Abuse and Mental Health Services Administration (SAMHSA). The survey collects data on the use, misuse and abuse of licit and illicit drugs among household residents.

NSDUH does not administer a dextromethorphan specific question; however, a series of questions on non-medical use of OTC cough and cold medicine was added in 2006.<sup>1</sup> The lead-in question asks “have you ever, even once, take a non-prescription cough or cold medicine just to get high?” A follow-up question asks about time of last use. Since not all OTC cough and cold medicines contain dextromethorphan, this question and its time of use follow-up represent a proxy for dextromethorphan abuse and are likely to over-state abuse of the ingredient.

As shown in *Table 2*, among respondents 12 or older, 0.6% reported use of OTC cough and cold products in the past year to get high. This compares to 4.8% for opioid pain relievers, and 10.3% for marijuana. The highest reported rates for

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<sup>1</sup> NSDUH includes sequences of follow-up, open-ended, non-medical use questions after broad drug categories (i.e., stimulants, pain relievers, etc.). Respondents use these open-ended questions to add other drugs they have used non-medically. Information on lifetime non-medical use of dextromethorphan can be assessed by these means. Lifetime use is not included in this section for three reasons. We do not know the respondent's age at time of use for this measure. Non-medical use captures a wider range of responses than does a response to a specific abuse question (ie, “to get high”). Using past year use reduces the opportunity for recall bias. More information on lifetime non-medical use is included in an eight-factor analysis in preparation from Pinney Associates, and in a NSDUH report, *Misuse of Over-the-Counter Cough and Cold Medications among Persons Aged 12 to 25*, SAMSHA, 2008.

non-medical use of marijuana and opioid pain relievers are in the 18-25 year old age group, in contrast to OTC cough and cold, where the highest rates are in the 12-17 year old age group.

**Table 2.** Percentage of respondents reporting past year use of OTC cough and cold products “to get high,” marijuana use, and prescription pain medicine non-medical use (NSDUH 2008).

	OTC cough/cold	Marijuana	Rx pain (opioids)
Age:	past year	past year	past year
12 to 17 years	1.8	13	6.5
18-25	1.5	27.6	12
26+	0.4	7	3.3
All ages	0.6	10.3	4.8

2008 National Survey on Drug Use & Health, SAMHSA.

As seen in *Table 3*, among those ages 12-18, rates of OTC cough and cold product abuse in the past year are in the range of 8 to 16 times higher for those using comparator substances contrasted with their peers who do not report non-medical use of the comparator substance in the past year, speaking to the prevalence of polydrug abuse among those who OTC cough and cold products “to get high.”

**Table 3.** Percentage use of OTC cough and cold products to get high among those who have used other drugs, ages 12-18 (NSDUH, 2008).

OTC Cough and Cold Products: Percentage of Use	
	Past Year
<u>Cigarettes</u> : Past year use	6.4%
No past year use	0.6%
<u>Alcohol</u> : Past year use	4.1%
No past year use	0.4%
<u>Marijuana</u> : Past year use	7.0%
No past year use	0.8%
<u>Hallucinogens</u> : Past year use	18.4%

OTC Cough and Cold Products: Percentage of Use	
	Past Year
No past year use	1.1%
<u>Tranquilizers</u> : Past year use	22.1%
No past year use	1.3%
<u>Rx Pain Relievers</u> : Past year use	14.7%
No past year use	0.7%

NSDUH 2008 analysis on file, Pinney Associates

#### 4.1.3.2 Monitoring the Future

Monitoring the Future (MTF, 2006-2009) is an investigator-initiated study conducted by the University of Michigan's Institute for Social Research. It has been funded since its onset in 1975 by the National Institute on Drug Abuse (NIDA) under a series of peer-reviewed, competitive research grants.

Monitoring the Future finds that more than 5% of 8<sup>th</sup>, 10<sup>th</sup>, and 12<sup>th</sup> graders have used OTC cough and cold medicine "to get high" in the past year. Among these persons, 48% report use 1-2 times and fewer than 1 in 80 have used these types of products "to get high" more than 5 times in the past year. (MTF 2008.) Use is not evenly distributed across adolescents, but is particularly concentrated among those who use alcohol, tobacco, and/or marijuana. The factors that discourage use to get high among adults and youth alike may be better understood than the factors that foster such use and abuse. For example, production of strong CNS effects (desired and undesired, such as dysphoria) requires dosages that are often nearly as high as doses that produce nausea and vomiting (Zawertailo 1998; internet monitoring analysis on file, Pinney Associates 2010). This is well known and discussed on Internet websites frequented by polydrug abusers who frequently warn of such effects (Internet monitoring analysis on file, Pinney Associates 2010).

Monitoring the Future first asked a question on use of nonprescription cough or cold medicines "to get high" in 2006. The survey specifically asks: "During the last 12 months, on how many occasions (if any) have you taken a non-prescription cough or cold medicine (robos, DXM, etc.) to get high?" Since not all OTC cough and cold medicines contain dextromethorphan, this question represents a proxy for dextromethorphan abuse and is likely to over-state abuse of the ingredient.

The use of the slang modifier “robos” or the abbreviation “DXM” in clarifying or limiting the question has not been tested. Results to this question through the four years it has been asked of 8<sup>th</sup>, 10<sup>th</sup>, and 12<sup>th</sup> graders are presented in *Table 4*. Prevalence shows some signs of decline in 8<sup>th</sup> and 12<sup>th</sup> graders, but an increase in 10<sup>th</sup> graders.

**Table 4.** *Over-the-Counter Cough/Cold Medicines: Trends in Annual Prevalence of Use (to Get High) in Grades 8, 10, and 12 (MTF 2006-2009).*

<b>OTC Cough/Cold Medicines</b>	<b>2006</b>	<b>2007</b>	<b>2008</b>	<b>2009</b>
8 <sup>th</sup> graders	4.2%	4.0%	3.6%	3.8%
10 <sup>th</sup> graders	5.3%	5.4%	5.3%	6.0%
12 <sup>th</sup> graders	6.9%	5.8%	5.5%	5.9%

For comparison, in the Monitoring the Future 2008 and 2009 studies, 2.5% of 8<sup>th</sup> graders, 8.1% of 10<sup>th</sup> graders, and 9.7% of 12<sup>th</sup> graders reported the abuse of Schedule III opioid Vicodin preparations within the past year (MTF 2008, 2009), underscoring that scheduling alone is not a guarantee of stopping abuse.

Consistent with the NSDUH findings, Monitoring the Future respondents who report abuse of OTC cough medicine are far more likely to abuse other substances compared to their peers who do not abuse the comparator substances, as shown in *Table 5*.

**Table 5.** Use of cough and cold medicine to get high in the past year by those using other drugs, by grade (MTF 2008).

		8 <sup>th</sup> Grade	10 <sup>th</sup> Grade	12 <sup>th</sup> Grade
Cigarettes:	30 Day, any use	19.3%	19.2%	12.3%
	No 30 day use	2.4%	3.4%	3.8%
Alcohol:	Annual use	8.6%	9.1%	7.3%
	No annual use	1.0%	1.4%	1.8%
Marijuana/Hashish:	Annual use	17.2%	15.2%	11.6%
	No annual use	1.8%	2.2%	2.1%
LSD:	Annual use	40.1%	47.6%	37.5%
	No annual use	3.0%	4.5%	4.7%
Sedatives:	Annual use	35.6%	32.9%	29.9%
	No annual use	1.9%	3.5%	3.9%
Tranquilizers:	Annual use	34.4%	36.8%	30.4%
	No annual use	2.5%	3.8%	3.9%
Other Narcotics:	Annual use	—	—	23.5%
	No annual use	—	—	3.5%
OxyContin:	Annual use	50.5%	47.8%	42.2%
	No annual use	2.4%	3.7%	3.6%
Vicodin:	Annual use	45.0%	37.5%	28.8%
	No annual use	2.2%	3.1%	3.0%
Inhalants:	Annual use	17.3%	30.8%	40.8%
	No annual use	2.2%	3.8%	4.7%

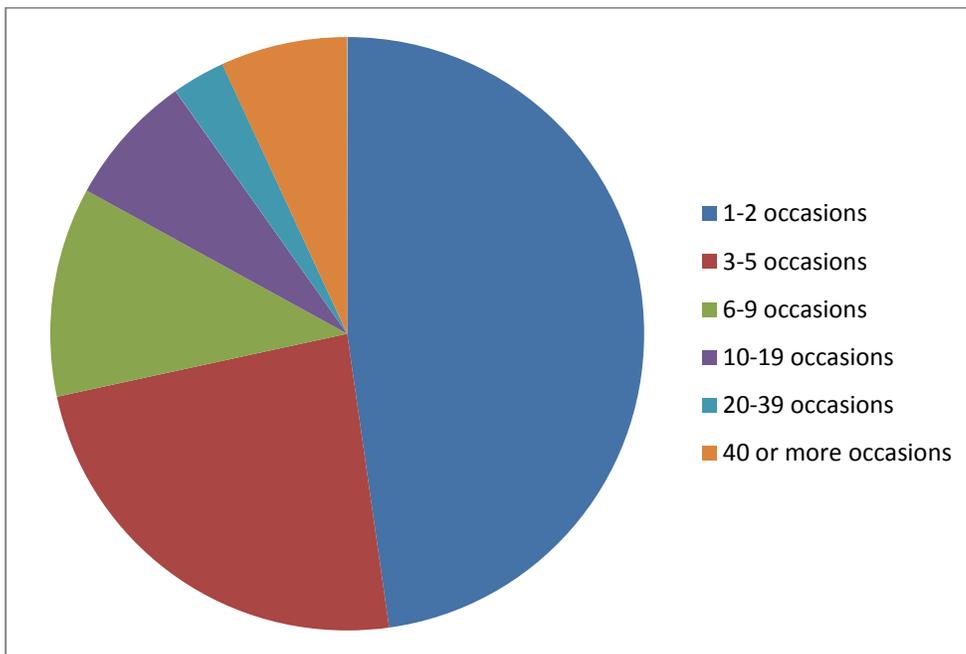
Table 6 and Figure 4 provide results on the frequency of abuse: in tabular form for all respondents, and in figure form among those reporting abuse. 48% of teens reporting abuse report using on one or two occasions in the past year.

**Table 6.** Frequency of Use of Nonprescription Cough and Cold Medicines to Get High (8<sup>th</sup>, 10<sup>th</sup>, and 12<sup>th</sup> Graders) (MTF 2008).

<i>“During the LAST 12 MONTHS, on how many occasions (if any) have you taken a nonprescription cough or cold medicine (robos, DXM, etc.) to get high?”</i>			
	8 <sup>th</sup> Grade	10 <sup>th</sup> Grade	12 <sup>th</sup> Grade
0 occasions	96.4%	94.7%	94.5%
1-2 occasions	1.6%	2.4%	3.0%
3-5 occasions	0.8%	1.2%	1.3%
6-9 occasions	0.2%	0.9%	0.5%
10-19 occasions	0.3%	0.4%	0.4%
20-39 occasions	0.2%	0.1%	*
40 or more occasions	0.4%	0.3%	0.3%
<i>Approximate weighted N =</i>	<i>5,200</i>	<i>5,000</i>	<i>4,700</i>

\* Estimate less than 0.1% has been suppressed.

**Figure 4.** Approximate Frequency of Use of Nonprescription Cough and Cold Medicines to Get High among Those Who Have Used, Combined 8<sup>th</sup>, 10<sup>th</sup>, and 12<sup>th</sup> (MTF 2008).



### 4.1.3.3 National Forensic Laboratory Information System

The National Forensic Laboratory Information System (NFLIS) is managed by the U.S. Drug Enforcement Administration (DEA). NFLIS looks at drug analyses from state and local forensic labs for controlled and non-controlled substances seized in law enforcement operations. NFLIS includes data from forensic labs that handle over 88% of the nation's nearly 1.2 million annual state and local drug analysis cases. In a given law enforcement case, any drugs seized in the case are listed as exhibits. Data obtained for the period of 2004-2008\* from NFLIS are shown in Table 7 below.

**Table 7.** NFLIS Data for dextromethorphan from state and local laboratories\*\* (2004-2008\*) (DEA 2009).

Year	Exhibits (and percentage of all exhibits for the time period)***
2004	62 (<0.01%)
2005	112 (0.01%)
2006	75 (<0.01%)
2007	67 (<0.01%)
2008*	60 (0.01%)

\* As of June 30, 2008

\*\*Data cannot be trended as the number of laboratories reporting is increasing with time.

\*\*\* Amount of drug substance not specified

### 4.1.4 Significance of Abuse

Databases which examine outcomes, including substance abuse treatment admissions or emergency room visits for non-medical use of dextromethorphan, reflect measurable but comparatively low levels of negative health outcomes from reported abuse. They also provide further support to the findings on the pattern and reported level of abuse discussed in section 4.1.3 that teens and young adults who abuse OTC cough products appear to discontinue such abuse in adulthood. Finally, these databases align with the review of literature summarized in Section 4.1.2, which did not identify any pre-clinical or clinical studies of dextromethorphan withdrawal or tolerance.

#### **4.1.4.1 Treatment Episode Data Set**

The Treatment Episode Data Set (TEDS), run by the Substance Abuse and Mental Health Services Administration, measures trends in substance abuse treatment admissions. TEDS includes all OTC medicines as a class, “including aspirin, cough syrup, diphenhydramine and other antihistamines, sleep aids, and any other legally obtained nonprescription medication.” (SAMHSA 2009.) Even using the OTC class as a proxy for dextromethorphan, which would overstate dextromethorphan treatment admissions, TEDS data presented in *Table 8* shows that OTC medicines accounted for 8,653 (< 0.05%) of the 20 million total TEDS admissions between 1998 and 2008. In comparison, non-heroin opioids accounted for 624,996 (approximately 3.1%) and non-methamphetamine stimulant admissions totaled 170,024 (or about 1% of all admissions) of TEDS admissions over the same time period.

The second point of note from TEDS is the stark contrast between the escalating rise of admissions due to abuse of opioids other than heroin, which increased every year from 1998 to 2008, contrasted with admissions due to all OTC products, which remained within a range of 482 to 1,085 through the period, with no clear trend.

**Table 8.** Admissions Aged 12 and Older by Primary Substance of Abuse: TEDS 1998-2008

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total:	1,704,606	1,715,336	1,750,426	1,767,430	1,885,044	1,861,305	1,818,357	1,886,466	1,920,147	1,870,351	1,893,640
<u>Opiates:</u>	266,658	279,717	298,301	314,859	330,016	326,163	322,635	330,105	347,549	341,680	378,586
Heroin	246,788	257,208	269,967	277,243	284,200	273,567	261,312	259,630	265,962	248,061	267,335
All Other Opiates	19,870	22,509	28,334	37,616	45,816	52,596	61,323	70,475	81,587	93,619	111,251
<u>OTC:</u>	482	1,085	763	616	634	704	827	768	915	829	1,030

Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS). Data received through August 31, 2009.

#### 4.1.4.2 DAWN

The Drug Abuse Warning Network (DAWN), administered by the Substance Abuse and Mental Health Services Administration (SAMHSA), monitors drug-related emergency department (ED) visits from a nationally-representative sample of general, non-federal hospitals with 24-hour emergency departments.

In general, DAWN does not publish statistical reports related to emergency department (ED) visits involving dextromethorphan. A 2006 DAWN Report, however, detailed ED visits from 2004 involving dextromethorphan. Details on 2006 dextromethorphan ED visits are also available, as are tables on antitussives as a class.

As seen in *Table 9*, an estimated 16,858 ED visits involved pharmaceuticals containing dextromethorphan. This was just under 1% of all drug-related ED visits. Of the 16,858 total dextromethorphan-related ED visits, 5,957 (35%) were associated with non-medical use, the broader category into which abuse falls, including over-medication, malicious poisoning, and “other.”

Consistent with what would expect from reported use of OTC cough and cold products “to get high” in NSDUH, as seen in *Table 9*, the rate of ED visits involving non-medical use of dextromethorphan was highest in those aged 12 to 20: 8.0 visits per 100,000 population, compared with 2.5 visits or fewer per 100,000 for other age groups. ED patients aged 12 to 20 accounted for about half (51%) of the ED visits resulting from non-medical use of dextromethorphan, compared with 33% of dextromethorphan-related ED visits overall.

**Table 9.** ED visits involving dextromethorphan, by age and reason for visit.

Age category	Estimated ED visits	Percent of visits <sup>a</sup>	ED visits per 100,000 population
<b>Non-medical use (35% of total)</b>			
0-11	42	1%	0.1
12-20	3,016	51%	8.0
21-34	1,451	24%	2.5
35+	1,448	24%	1.0
<b>Medical use (adverse reaction) (31% of total)</b>			
0-11	1,879	36%	3.9
12-20	744	14%	2.0
21-34	682	13%	1.2
35+	1,890	36%	1.3
<b>Accidental ingestion (15% of total)</b>			
0-11	2,478	96%	5.2
12-20	—	0%	0.0
21-34	—	0%	0.0
35+	109	4%	0.1

Age category	Estimated ED visits	Percent of visits <sup>a</sup>	ED visits per 100,000 population
<b><i>Suicide attempt (17% of total)</i></b>			
0-11	—	0%	0.0
12-20	1,610	55%	4.3
21-34	527	18%	0.9
35+	778	27%	0.5
<b><i>Total b</i></b>			
All ages	16,858	100%	5.7
0-11	4,399	26%	9.2
12-20	5,556	33%	14.7
21-34	2,662	16%	4.7
35+	4,236	25%	2.8

a Percentages may not sum to 100 percent due to rounding.

b This total includes only the four types of ED visits shown. This excludes patients who go to the ED to obtain admission to a hospital's detoxification or substance abuse treatment unit.

Note: — Estimates less than 30 are suppressed.

Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2004 (March 2008 update).

In 2006, drugs containing dextromethorphan were involved in an estimated 10,117 non-medical use of pharmaceutical ED visits. This represented a 70% increase from 2004, when dextromethorphan was involved in 5,957 non-medical use ED visits.

DAWN data can also be searched by criteria. A search of the analytic category "all misuse and abuse" within DAWN 2004-2008 tables provides results for the class of antitussives, in which dextromethorphan is the most common. Using this method, as shown in *Table 10*, antitussives were involved in 0.18% of ED visits in the drug misuse and abuse visit group in 2008. This represents an increase from 0.14% in 2004. A majority of the ED visits involving dextromethorphan were multi-drug, ranging from 77% to 57% over the 5-year period. *Table 11* presents this same information by rate per 100,000 population.

**Table 10.** DAWN 2004-2008 Analytic group: Drug misuse and abuse visits, antitussive estimates by year (SAMSHA; accessed August 14, 2010).

	Estimates 2004	Est. 2005	Est. 2006	Est. 2007	Est. 2008
Total ED visits for analytic group	1,619,054	1,616,311	1,742,887	1,883,272	1,999,861
Total drug reports	2,853,661	2,821,037	3,086,984	3,335,348	3,667,298
Antitussives	2,411	2,568	3,174	3,067	3,584
Multiple drugs, including an antitussive	1,856	1,934	2,150	1,801	2,054

**Table 11.** DAWN 2004-2008 Analytic group: Drug misuse and abuse visits, antitussive rates per 100,000 population by year (SAMSHA; accessed August 14, 2010).

	Rate 2004	Rate 2005	Rate 2006	Rate 2007	Rate 2008
Total ED visits for analytic group	552.8	546.9	584.1	625.1	657.7
Total drug reports	974.3	954.5	1034.6	1107.0	1206.1
Antitussives	0.8	0.9	1.1	1.0	1.2
Multiple drugs, including an antitussive	0.6	0.7	0.7	0.6	0.7

#### 4.1.4.3 Other Means to Assess Significance of Abuse

CHPA has retained the Rocky Mountain Poison and Drug Center to evaluate additional data to measure the significance of dextromethorphan abuse, including serious adverse events with dextromethorphan involving overdose or an abuse-containing term. This evaluation was not completed at the time of this briefing book's submission. It will be provided separately to FDA, and included within a September 14, 2010, advisory committee presentation.

#### 4.1.5 Risk and Benefit to Public Health

Dextromethorphan has a long history of use, and is well-tolerated when used as directed. At doses recommended for cough suppression, dextromethorphan has no effect on respiration, the cardiovascular system, the gastrointestinal tract, or mucociliary activity. Also, it has little or no sedative and analgesic action (FDA 1976, Karttunen 1990, Bem 1992, Siu 2007).

Intentional abuse of dextromethorphan has been reported over time; however, national surveys indicated the incidence of such abuse is low and relatively constant, even given widespread availability of the products. Abusers are predominantly teens or young adults who also tend to abuse other substances. In general, health consequences of dextromethorphan abuse appear infrequent and not serious, but can lead to morbidity, emergency room visits, and, in very rare instances, death (Chyka 2007, Bem 1992).

Public health risks of a substance must be considered from the perspective of benefits. Given that 133 million packages of dextromethorphan-containing OTC cough suppressants are sold annually, and more than 36% of American households use these medicines to relieve cough each year, the public health burden of low level abuse is far outweighed by the products' health benefits.

Conversely, scheduling dextromethorphan would have a potential *negative* public health impact by limiting access for those who have a legitimate need to relieve their cough. Scheduling dextromethorphan would impose significant barriers to access for those seeking relief for cough. Depending on the schedule, these barriers range from requiring a physician visit to obtain a prescription for medicines with the ingredient, to requiring a prescription in at least 18 states and severely restricting the number of outlets which may distribute the medicine in all other states through pharmacist-only dispensing and record-keeping requirements. OTC access to dextromethorphan-containing products provides a public health benefit by allowing self-treatment of acute cough, saving doctor visits and prescription costs.

In the absence of suitable OTC products, people with cough are more likely to seek physician care. If one in ten people currently using an OTC cough medicine visited a doctor instead, it would result in eight million additional doctor visits in a 3-month period (Michaels Opinion Research 2007), adding to the rapid growth of healthcare costs. It is estimated that self-treatment of cough and cold symptoms saves \$4.75 billion/year in the U.S. as a result of improved work productivity and reduction in use of prescription medicines and doctor visits (Lipksy 2004). In the Department of Health and Human Services' response to a World Health Organization questionnaire concerning dextromethorphan, the Department concurred that a prescription requirement for dextromethorphan-containing medicines would likely result in increased utilization of the healthcare system, with a likely increase in healthcare costs as a result (FDA 2008).

#### **4.2 Conclusions of the Analysis of Abuse Potential**

CHPA does not believe scheduling of dextromethorphan is warranted. This conclusion is based on a totality review of the data from a number of aspects:

**Pharmacology and abuse potential studies:** Clinical studies find that, at high doses, dextromethorphan can exert mixed clinical effects, eliciting both euphoria and dysphoria. These effects are often associated with nausea and vomiting, as well as "disliking" sensations in abuse liability evaluations. Dysphoria and "disliking" increase dose-dependently. These effects suggest a low potential for chronic abuse.

Withdrawal or tolerance do not appear to be factors in misuse and abuse of dextromethorphan. There are no controlled pre-clinical or clinical studies demonstrating that dextromethorphan produces physical dependence as measured by tolerance or withdrawal, however, there are isolated case reports suggesting it may produce psychological dependence.

**Data on prevalence of reported abuse of OTC cough and cold medicine from national, government-sponsored surveys:** National surveys show the abuse of OTC cough medicines, including those which contain dextromethorphan, is limited in its prevalence and scope. Abuse appears to be concentrated among teens and, to a lesser degree, young adults, particularly those with histories of alcohol, marijuana and/or tobacco use. Nonmedical use and abuse outside of these populations appears to be rare. Overall abuse patterns are flat over the four years for which national data is available.

**Outcomes databases:** Substance abuse treatment admissions and emergency room visits for overdose resulting from non-medical use reflect measurable but low levels of negative health outcomes from reported abuse or misuse. They also provide further support to the findings on the pattern and reported level of abuse in survey findings that teens and young adults who abuse OTC cough products appear to discontinue such abuse in adulthood. These databases align with the review of literature on pharmacology and clinical studies which did not identify any pre-clinical or clinical studies of dextromethorphan withdrawal or tolerance.

An analysis of serious adverse events related to dextromethorphan involving abuse or overdose is forthcoming.

While measurable abuse of OTC cough medicines, most of which contain dextromethorphan, does occur, this abuse should be viewed in the context of the ingredient's widespread use for over 50 years as a safe, effective cough suppressant. As discussed in Section 5, there are more targeted interventions to reduce OTC cough medicine abuse, particularly among teens, *without* scheduling:

- Educational interventions tailored to directly impact specific goals of raising parent awareness, increasing the perception of risk among teens, and increasing social disapproval of the behavior; and
- Legislative initiatives to address accessibility by teens through a national age restriction on purchase and to establish a prohibition on sale of the unfinished ingredient to those not registered with FDA.

## **5. Reducing Dextromethorphan Abuse Through Evidence-Based Interventions**

The OTC medicine industry, through CHPA coordination, has an established history as a leader in developing long-term, evidence-based interventions and assessments to reduce abuse of dextromethorphan and dextromethorphan-containing over-the-counter cough medicines. The industry's efforts have evolved and grown over time as new data have become available. CHPA member companies that sell a dextromethorphan-containing medication are involved in these efforts and is committed to ensuring that none of their medications are abused.

The industry has taken the best insights and practices from knowledgeable experts in addressing cough medicine abuse prevention, which means addressing the factors that impact the behavior and using research to inform appropriate interventions. Because the data show a higher prevalence of abuse of dextromethorphan among teens, industry's interventions are largely targeted towards influencing this demographic. While teen substance abuse is a very complex behavior, an examination of published literature points to a number of key factors, including low parental awareness, low perception of risk, low social disapproval, and ready availability as key factors impacting substance abuse potential.

The industry's programming to-date has been focused on addressing these risk factors in a step-wise, evidenced-based approach, starting with addressing low parental awareness and advocating for educational and legislative vehicles to reduce the availability of dextromethorphan to teens. CHPA's programs will continue to grow with interventions designed to increase both teens' perceptions of risk about cough medicine abuse and the social disapproval of this type of abuse. These latest interventions, which will launch in 2011, will include a comprehensive digital media program directly targeted at teens. (See section 5.3.2.)

Overall, the industry's intervention strategies to mitigate dextromethorphan abuse are designed to impact teens' entire environment by targeting the following goals:

- **Raise parental, caregiver, and teen-influencer awareness and involvement as to the abuse and its risks;**
- **Increase the perception of risk among teens by highlighting the risks of abuse;**
- **Increase social disapproval of the behavior by emphasizing peers' disapproval of abuse and demonstrating that non-abuse is the norm;** and

- **Reduce dextromethorphan's availability to teens by:**
  - Advocating for legislation to establish a national age restriction on purchases of dextromethorphan-containing medicine;
  - Advocating for legislation to prohibit the sales of bulk, unfinished dextromethorphan to parties not registered with FDA; and
  - Encouraging parents and caregivers to engage in monitoring behaviors, such as safeguarding their medicine cabinets, and making sure other parents do likewise.

CHPA's goals, interventions, and assessments are informed by quantitative prevalence data, qualitative research into the attitudes and behaviors of the abuser, and proven strategies and recommendations from leading substance abuse prevention experts.

As previously mentioned, CHPA's targeted interventions are following a step-wise implementation of elements and tools. This allows for the acquisition of still-evolving prevalence and attitudinal data, and the development and refinement of sound educational strategies matched against clearly outlined goals to change attitudes, perceptions, and ultimately behaviors, and thereby reduce abuse rates.

To accomplish this, CHPA:

- Enlisted the full sponsorship of participating OTC member companies;
- Engaged various stakeholders, especially the Partnership for a Drug-Free America (the Partnership), government agencies, prevention experts, and healthcare professionals;
- Proposed national legislation to restrict the availability of bulk, unfinished dextromethorphan from non-FDA registered entities and dextromethorphan-containing medicines from teens under the age of 18 years;
- Supported the inclusion of OTC cough medicine abuse rates in national survey instruments, including the Partnership Attitude Tracking Survey (PATS) and Monitoring the Future (MTF);
- Supplemented research to better understand the attitudes and behaviors of the dextromethorphan abuser; and
- Developed and implemented, in consultation with substance abuse professionals, a communications plan for targeted, evidence-based educational programming with tested messaging and ongoing assessment.

The early stages of this effort, which focused on data collection and addressing low parental awareness, began in 2003. When the first data from national surveys including cough medicine abuse became available in 2005-2006, the industry stepped up its programming based on expert recommendations, and has increased interventions, especially those focused on parents, with evolving and expanding programming each subsequent year. As additional tools for parents,

CHPA also has been working to pass federal legislation to address both the availability of cough medicines to teens and the overall access to bulk, unfinished dextromethorphan to non-FDA registered entities. It bears noting that teens were not a primary initial target of the industry's programming since experts and government agencies cautioned CHPA against targeting teens directly for fear of over-exposing teens otherwise unaware of the abuse potential.

Because of research CHPA commissioned in 2010, CHPA, along with the Partnership for a Drug-Free America, is comfortable designing a program targeted at teens and feels confident in implementing a well-targeted teen program. This component of the abuse mitigation plan is discussed in detail in Section 5.3.2 and provides for a comprehensive intervention strategy to help reduce dextromethorphan abuse.

## 5.1 Overview of Dextromethorphan Abuse

In understanding the abuse of dextromethorphan and in developing strategies towards its prevention, as discussed in Section 4.1.3 concerning patterns of reported abuse, it is important to look at the context and demographics of the reported abuse. The first contextual element to note is that this is abuse, not misuse, and is intentional; i.e., teens and young adults taking doses well above the therapeutic dose and for purposes other than those labeled on the Drug Facts label.

The data from qualitative research conducted by the Partnership for a Drug-Free America in 2010, along with existing prevalence data, provide key insights to the scope of abuse and strategies to prevent abuse.

- **Dextromethorphan abuse is limited in its prevalence and scope.**  
While CHPA and its member companies believe any abuse is too much, the number of teens abusing cough medicine is small, with five percent of 8<sup>th</sup>, 10<sup>th</sup>, and 12<sup>th</sup> graders reporting having abused it at least once in the past year (MTF 2009). Approximately half of teens who report abusing dextromethorphan do so only one or two times (MTF 2008). The Partnership's 2010 qualitative research suggests strongly that many, if not most, teens who try abusing dextromethorphan stop after abusing once or twice because the high is unpleasant and unsatisfactory.
- **The physical effects from abusing dextromethorphan are not desirable.**  
Abusers report the poor quality of the effects of large doses of dextromethorphan (Partnership 2010, Internet monitoring analysis, Pinney Associates 2010). The negative effects of exposure to high doses of dextromethorphan include dysphoria, nausea, blurred vision, and disorientation (Zawertailo 1998, SAMHSA 2006, Internet monitoring

analysis, Pinney Associates 2010). Not only is this a powerful abuse prevention tool but also can explain why many kids who try cough medicine only abuse it once or twice before quitting. Moreover, the almost universally held image of the teen cough medicine abuser is that of a “loser,” not an aspirational figure (Partnership 2010).

- **Dextromethorphan abusers are already engaged in substance abuse behaviors.**

National surveys such as the Monitoring the Future Study and the National Survey on Drug Use and Health (NSDUH) indicate that OTC cough medicine abuse is most common among teens who also smoke cigarettes, drink alcohol, and abuse other drugs. For example, teens and young adults who self identify as abusing dextromethorphan also report abusing a cadre of illegal substances, including marijuana and prescription drugs, at rates far higher than their peer group at large (MTF 2008, NSDUH 2008). It is also important to note that the Partnership’s research shows two types of abusers: experimental drug users who try dextromethorphan one or two times and stop, and the more serious, troubled drug user (PATS 2009, Partnership 2010).

- **OTC cough medicine abuse has remained relatively flat.**

The incidence of abuse of OTC cough medicine has remained relatively flat since consistent data have been collected. In addition to stable prevalence reports, treatment centers and emergency departments report low rates of abusers (MTF 2006-2009, TEDS, DAWN). In designing preventive interventions, therefore, one consideration in CHPA’s efforts has been to avoid any actions that could inadvertently fuel increased attractiveness to dextromethorphan abuse.

As with any substance abuse issue, dextromethorphan abuse is serious and requires a long-term, targeted prevention approach. The general concentration of dextromethorphan abuse in teens provides a basis for targeted interventions to help reduce such abuse and minimize the unintended consequences resulting from abuse.

## **5.2 The Effectiveness of Education to Reduce Substance Abuse**

### **Targeted education has been shown to be the most effective intervention at reducing substance abuse.**

In designing an effective education-based intervention to reduce substance abuse, it is important to look at the understood and well-studied factors impacting decisions and behaviors toward abuse.

**Research from multiple sources shows that substance abuse among teens is a complicated interaction between a host of risk and controlling factors.**

Risk factors are those that may put a person more at risk for abuse. Controlling factors are those that have been shown to impact an individual's decision not to abuse drugs. Risk factors include:

- Awareness to the abuse potential of a particular substance and perceptions about that substance's alleged benefits
- Risky personality traits, such as sensation-seeking tendencies
- Familial strife, such as divorce
- Mental health issues
- Perceived availability to the drug in question
- Social variables, such as a misperception about the prevalence of abuse

Controlling factors include:

- Perception of risk
- Social disapproval
- Parental awareness
- Involvement in adult-run institutions, like family, school, and religious institutions
- Role models, such as sports figures or actors whose real-life stories demonstrate the dangers of abuse

**The two attitudes that correlate most strongly with drug use are perception of risk and social disapproval** (Romer 2003). Substances that have a low perception of risk and low social disapproval more commonly have a higher abuse rate. Conversely, studies have shown that increasing the perception of risk about abusing a substance and its social disapproval have a large impact on reducing abuse. **Additionally, research shows that parental intervention, such as talking to teens about substance use, has a significant impact on a teen's decision to abuse drugs and alcohol** (PATS 2009). Many successful education-based interventions, including those focused on tobacco, alcohol, inhalants, Ecstasy, and heroin, have utilized strategies to address perception of risk, social disapproval, and parental awareness. Detailed examples of successful education interventions for inhalants and Ecstasy can be found in Appendix 3.

### **5.3 Comprehensive Dextromethorphan Abuse Mitigation Plan**

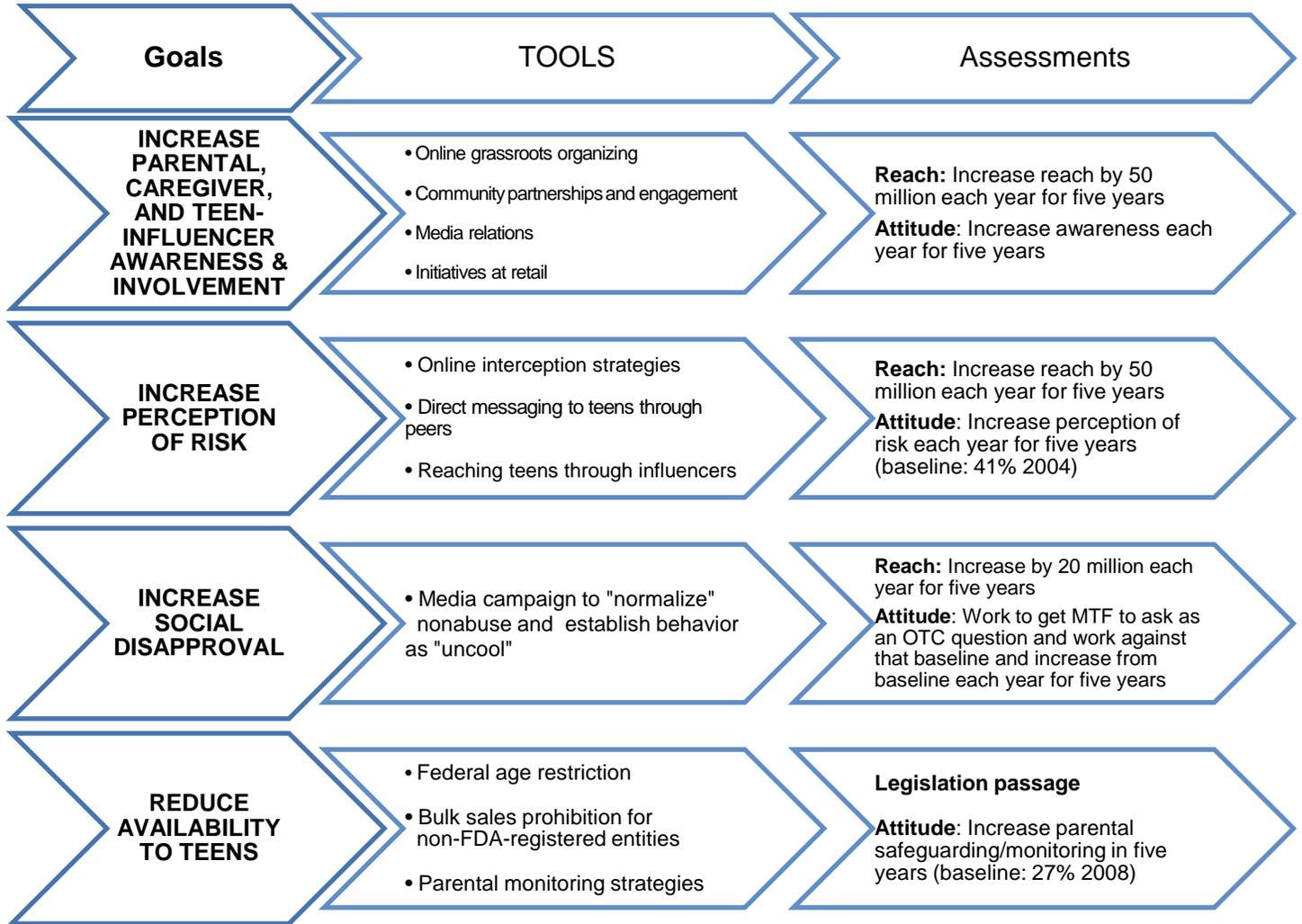
The OTC drug industry, through CHPA coordination, has undertaken a long-term approach and commitment to help prevent the abuse of cough medicine (See Appendix 1 for a timeline of CHPA activities related to cough medicine abuse) with an active, ongoing, and evolving education strategy targeting abusers and their parents, aligned with key partners who have demonstrated success in implementing evidence-based intervention programs.

CHPA developed a strategic plan to prevent teen cough medicine abuse through a stepwise approach to raise awareness in order to change attitudes and perceptions and thereby change behaviors. This program has evolved as new data have become available. (The phases of this program are outlined in Section 5.3.2.) Because there were very limited data on dextromethorphan abuse, CHPA made it a priority to understand as much as possible about this abuse so that the right interventions could be employed *without* over-exposing the abuse potential to teens. To that end, the industry's program began with data collection and information-sharing with experts, expanded to direct and aggressive outreach to parents, caregivers, and other teen influencers, and will grow in 2011 to directly reach teens in a far more substantial and proactive manner now that additional information is available to target this audience.

As previously stated, the goals of the targeted interventions to mitigate dextromethorphan abuse are:

- **Raise parental, caregiver, and teen-influencer awareness and involvement as to the abuse and its risks;**
- **Increase the perception of risk among teens by highlighting the dangers of abuse;**
- **Increase social disapproval of the behavior by emphasizing peers' disapproval of abuse and demonstrating that non-abuse is the norm;** and
- **Reduce dextromethorphan's availability to teens by:**
  - Advocating for legislation to establish a national age restriction on purchases of dextromethorphan-containing medicine;
  - Advocating for legislation to prohibit the sales of bulk, unfinished dextromethorphan to parties not registered with FDA; and
  - Encouraging parents and caregivers to engage in monitoring behaviors, such as safeguarding their medicine cabinets, and making sure other parents do likewise.

**Figure 5.** The industry’s interventions are designed to align against four goals, utilizing proven, effective tools to disseminate information, engage stakeholders, and change attitudes. All messaging is grounded in research. Assessments exist to help gauge resonance and effectiveness against goals.



### 5.3.1 Target Audience of Dextromethorphan Abuse Mitigation Plan

The mitigation plan is targeted toward parents, caregivers, and teen influencers, and teens. Since parental awareness and involvement is a controlling factor related to abuse rates, the large majority of our programming has been focused on outreach to parents. Parents are optimally positioned not only to monitor their teens’ behaviors but also communicate knowledgeably about the dangers of abuse and set standards of acceptable behaviors for their homes. An aware and engaged parent is a highly effective influencer on whether a teen is drug-free. In

fact, teens who learn a lot about the risks of drugs are up to half as likely to abuse drugs (PATS 2009). CHPA's education and outreach programming targets parents, guardians, caregivers, and other teen influencers directly and through community leaders and institutions, such as healthcare professionals and schools. This outreach started in 2003 and is ongoing and expanding. (See Section 5.3.2 and Appendix 2 for more details.)

The next key audience is teens. While a small number of young adults do report abusing cough medicine, this abuse is relatively low and often involves a series of other substances (NSDUH 2008). The bulk of CHPA's teen-directed programming (See Section 5.3.2) will be focused on reducing and preventing teen abuse of cough medicine by targeting the at-risk and experimental users (roughly half of the five percent reported abuse). While it is important to reach all abusers of cough medicine, research shows that those who are abusing dextromethorphan five or more times are typically abusing a cadre of other substances at rates that far exceed their peer group (NSDUH 2008, MTF 2008). Of the substances they are abusing, dextromethorphan falls at the bottom of their preference list (Partnership 2010). Appropriate interventions for this population include individualized and timely mental health and medical health interventions to address their substance use.

### **5.3.2 Implementation of Dextromethorphan Abuse Mitigation Plan**

The foundation of the abuse mitigation plan is research and ongoing assessment targeted to the goals outlined in section 5.3. The implementation should be considered in terms of phases, each informed by data available at the time and expert recommendation, and each subsequent phase building on and expanding from the previous phase. Accordingly,

- The first phase, beginning in 2003, involves data collection to understand the issue and prevalence in order to craft appropriate, thoughtful, and successful interventions.
- The second phase, which began tentatively in 2003 and expanded greatly in 2006 and is ongoing, involves raising parental, caregiver, and teen-influence awareness and involvement, as well as advocacy designed to reduce the availability of dextromethorphan to teens.
- The third phase, which concluded August 2010, involves additional data collection, this time into the abusers' profile and attitudes governing abuse.
- The fourth phase, which will begin in 2011, is the point at which the industry and its partners in prevention will directly and environmentally target at-risk teens' perceptions and attitudes, bringing all the learnings and programming together from the previous phases.

## Phase I: Understanding the Issue and Prevalence

CHPA began working on cough medicine abuse when it started seeing a trend among teens to abuse pharmaceuticals and other synthetic drugs, along with anecdotal reports of cough medicine abuse. CHPA's first objective was to better understand the prevalence and attitudes surrounding dextromethorphan abuse. In conjunction with substance abuse experts and government agencies, including DEA and FDA, CHPA encouraged better ways to track the prevalence of cough medicine abuse at the national level. Since no prevalence or attitudinal data were collected on a national level, CHPA took a leading role in prompting the preeminent drug prevention stakeholders to include over-the-counter cough medicines in their existing drug abuse research. The first national surveys that included OTC cough medicine abuse were released in 2005 and 2006.

In 2005, the Partnership for a Drug-Free America released the first national survey data on teen nonprescription cough medicine abuse with its Partnership Attitude Tracking Survey (PATS). That first survey included self-reported lifetime abuse (one in 10 teens reporting having abused an OTC cough medicine to get high at least once in their lives) and perception of risk (41% perceived OTC cough medicine abuse to get high as risky) questions. PATS added a question in 2007 to get a better understanding of teens' perception of environmental prevalence (30% of teens reported they have friends who abuse cough medicine). In 2008, PATS added questions about past-year (7%) and past-30 day abuse (4%).

After the 2005 release of its PATS study, the Partnership for a Drug-Free America received a grant from CHPA to conduct a series of focus groups comprised of parents of teens to better understand parental attitudes and beliefs about this type of substance abuse. Those focus groups revealed a profound lack of knowledge among parents to teen cough medicine abuse and its risks.

The focus groups showed that parents fell into the following categories: unaware teens abuse cough medicines; aware of abuse generally but doubtful *their* teen would abuse ("not my kid"); or aware of abuse, but considered medicine abuse less worrisome and more acceptable than illicit drug abuse.

CHPA and the Partnership utilized these findings to help shape the first-ever media campaign targeted to building parental awareness about cough medicine abuse. (See Appendix 2 for details.)

In 2006 at the prompting of the Partnership for a Drug-Free America, Monitoring the Future added one question to determine self-reported past-year abuse of over-the-counter cough medicines. The initial survey showed that 4.2% of 8<sup>th</sup> graders, 5.3% of 10<sup>th</sup> graders, and 6.9% of 12<sup>th</sup> graders reported abusing over-the-counter cough medicines in the past year.

That same year and as part of a partnership with CHPA, the Community Anti-Drug Coalitions of America (CADCA) also surveyed its coalition leadership to determine its perceptions regarding the scope of the problem locally and the needs of its stakeholders including prevention specialists, law enforcement, retailers, healthcare professionals, and educators. The survey found 39 percent of coalition leaders indicated OTC medicine abuse was a major problem in their communities. After targeted awareness building, that number rose to 46% in 2008.

In 2008 CHPA conducted a national survey of parents to assess parental attitudes and behaviors regarding OTC cough medicines. In that survey, only 27% of parents reported monitoring their OTC cough medicines.

### **Phase II: Raising Parental, Caregiver, and Teen-Influencer Awareness & Involvement, and Advocating for Legislative Tools to Reduce the Availability of Dextromethorphan to Teens**

Parental awareness and involvement are powerful tools in tackling substance abuse among teens. Research shows that teens who learn a lot about the risks of drugs in the home are up to half as likely to abuse drugs (PATS 2009). Evidence also supports the assertion that parental monitoring and disapproval are key controlling factors for teens' decisions not to abuse substances (NSDUH 2008).

Prior to the efforts undertaken by industry, the minority of parents who actually were aware of this type of abuse believed it to be rare and relatively safe when compared to street drugs (Partnership 2005). Teens were not learning about the risks, and community stakeholders, including retailers, were generally not aware of the abuse. While other substance abuse issues, such as prescription drug abuse, inhalants, marijuana, or alcohol, received a great deal of media attention, cough medicine abuse remained relatively under the radar screen in most households.

Increasing parental awareness and involvement, therefore, is a primary objective of the industry's efforts to curb the teen abuse of OTC cough medicines containing dextromethorphan and was the initial focus of CHPA's educational interventions. Research clearly highlighted the need for increased parental awareness since many parents seemed unaware of this type of abuse and its associated risks or that substance abuse could happen in any home. Industry's efforts to raise parental awareness and involvement began by informing parents that teens can abuse, any teen might engage in abuse, and there are dangers associated with abuse.

CHPA developed a communications plan to impact attitudes and engage those in the community who either serve as message multipliers to parents or who are teen influencers.

CHPA's communications plan utilizes:

- Online communications,
- Media,
- Stakeholder engagement and partnerships,
- Retail programs, and
- Legislative initiatives.

Full details about CHPA's ongoing and expanding interventions are available in Appendix 2.

CHPA's current and ongoing interventions to-date include:

- Programs at point of purchase including the placement of an educational icon directly on the packages of dextromethorphan-containing cough medicines (See Appendix 2)
- Online campaigns such as the Five Moms Campaign and WebMD educational collaboration designed to provide information to parents and encourage behaviors like talking to teens about the dangers of cough medicine abuse, monitoring their medicine cabinets, and sharing information with other parents
- Multimedia public service announcements with the Partnership for a Drug-Free America
- Community programs such as the comprehensive partnership with the Community Anti-Drug Coalitions of America that include town hall meetings, online editorial and video content, printed brochures, etc.
- The "Home to Homeroom" Campaign with the National Association of School Nurses that utilizes one of the most accessible healthcare professionals—the school nurse—in prevention efforts targeted to both parents and their teens
- Community- and school-based programs with D.A.R.E. America to provide parents with information as well as lessons to 5th, 7th, and 9th graders
- DXMstories.com, an interception website developed with the Partnership for a Drug-Free America, to provide at-risk teens with information about the dangers of dextromethorphan abuse
- Promotion of a federal age restriction on the purchase of dextromethorphan-containing cough medicines
- Promotion of a federal prohibition on the sale of the bulk, unfinished dextromethorphan to non-FDA registered entities

**Table 12: Summary of Current and Ongoing Interventions (See to Appendix 2 for complete details.)**

	Misc	DXM Stories	CADCA programming, including the community toolkit and resources	Earned media	PSAs	Five Moms	Paid media	DARE America Program	Social Networking and Online Community Building	National Medicine Abuse Awareness Month	Educational Icon	WebMD Cough Medicine Abuse Educational Collaboration	Home to Homeroom with the National Association of School Nurses
Start:	2003	2003	2005	2005	2006	2007	2007	2007	2007	2007	2008	2009	2010
Parents	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hispanic Parents	✓			✓	✓	✓	✓			✓			
At-Risk Teens	✓	✓	✓					✓				✓	✓
Peers			✓					✓				✓	✓
Healthcare Professionals	✓		✓								✓		✓
Retailers	✓		✓								✓		
Educators/Schools	✓		✓					✓					✓
Law Enforcement	✓		✓					✓					
Resources Available	✓		✓		✓	✓		✓		✓		✓	✓
<b>REACH/ RESULTS</b>		665K	115 M adults 14 M students	70 M impr.	\$3.1 M ad equ. >1M brochures	35 M impr.	288 M impr.	1 M kids 350K parents			23.5 M Impr.	660 K visitors	1.4 M students

A component of CHPA’s mitigation plan involves reducing the availability of dextromethorphan to teens, both the finished product and the bulk, unfinished ingredient by aligning interventions towards their key access points: at retail, in the home, from friends, and to a far less extent online.

While the two variables with the greatest influence on teen substance abuse are perception of risk and social disapproval, CHPA and its member companies also believe there are interventions regarding access to teens specifically that can positively impact abuse, in addition to providing parents with more tools to monitor their teens’ behavior.

These interventions include both legislative and educational initiatives that the industry has supported and advocated for a number of years and will continue to be a key part of the overall abuse mitigation strategy. While it is true that data show that limiting the supply of a substance is not always directly related to limiting the abuse of that substance, the industry feels that certain restrictions on teen access are reasonable and potentially effective interventions because they are specifically targeted at the core abuse population and where abusers are

accessing the ingredient, and do so without placing an undue burden on parents and other adults in need of treatment options for cough. A summary of these ongoing efforts follows below.

- **Restricting access to dextromethorphan-containing medicines at retail through age restrictions. CHPA strongly believes that unrestricted adult access to dextromethorphan-containing medicines is important because of the individual and public health benefit, however, the association also believes that restricting teen access to these medicines is a reasonable and a potentially effective approach given the highest prevalence of abuse is among teens.** A number of national retailers have implemented voluntary age restrictions in their stores, but this is not the current national standard at point of purchase. While encouraging retailers to implement voluntary age restrictions, CHPA also has been strongly advocating for a national age restriction on the sale of OTC medications containing dextromethorphan since 2007. Legislation (S. 2274) was first introduced by then-Senator Biden along with three co-sponsors, Senators Grassley, Durbin, and Feinstein in October of 2007. The bill did not pass out of the Senate in 2008. Senator Durbin introduced a similar age restriction bill in 2009 (S. 1383) that was also co-sponsored by Senator Grassley and is currently pending in the Senate Judiciary Committee. While federal legislation is CHPA's preferred approach, the association has supported age restriction legislation on the state or local level in New Jersey and Nassau and Westchester Counties in New York.

Until such federal legislation is passed, CHPA supports and endorses ongoing retailer efforts to restrict sales of dextromethorphan-containing medicines to underage teens.

There are various examples of age restrictions having an impact on controlling teen use and reducing rates of teen use and abuse, including alcohol and cigarettes. The impact of the minimum legal drinking age had a significant impact on alcohol-related fatalities (National Institute on Alcohol Abuse and Alcoholism 2008). It bears noting that these legislative initiatives were supported extensively with educational interventions.

- **Restricting access to dextromethorphan in its bulk, unfinished form.** In 2003 CHPA read the first media report of death associated with bulk, unfinished dextromethorphan abuse. Additional sporadic reports surfaced in 2004 and 2005. Teenagers and young adults were reported to have accessed bulk, unfinished dextromethorphan from rogue Internet sites. FDA and law enforcement moved swiftly to shut these distributors and sites down and prevent further incidents. In one case, the U.S. government reached plea agreements with operators of an Internet company through which misbranded pure, powder dextromethorphan was sold. Defendants

admitted to knowing that 95 percent of their customers intended to ingest the dextromethorphan “to get high” and operated their website even after they learned that their dextromethorphan caused two deaths (FDA 2006).

As a result, CHPA has been advocating for national legislation to prohibit the sale of the bulk, unfinished form of the ingredient dextromethorphan to non-FDA registered entities since 2005. While it appears that efforts to shut down the selling of dextromethorphan in its bulk form have had an impact, CHPA believes there is no legitimate reason for a teen or anyone not working in medicine manufacturing or science/academia to possess it in unfinished form. H.R. 1259 has passed the U.S. House of Representatives for this purpose and is currently before the Senate.

- **Safeguarding medicines at home.** Because teens report accessing medicines, including cough medicine, from the home, it is important that parents and caregivers pay attention to the medicines in their medicine cabinet. One of the main messages in the industry’s parent outreach is to help curtail this primary teen access point to the ingredient. CHPA’s parental awareness campaign will continue to emphasize the importance of safeguarding medicines in the home.
- **Monitoring teens’ activities on the Internet and at friends’ homes.** Another integral component of reducing the ease by which teens have access to the ingredient is through parental monitoring. Parents need to be vigilant not just about their homes, but also who their teens are spending time with and what they are searching for on the Internet. Qualitative research shows that teens are researching drugs before abusing them and information gathered from websites on psychoactive plants and chemicals shows that these websites are providing detailed instructions on how to abuse medicines, including dextromethorphan-containing medicines, or on obtaining the bulk, unfinished form of dextromethorphan. A main component of CHPA’s parental awareness campaign is encouraging parents to monitor their teens’ Internet activities, as well as keeping current with their friends and friends’ parents.

### **Phase III: Understanding Abuser Attitudes and Behaviors**

To develop interventions to help influence teen perceptions of risk and social disapproval of dextromethorphan abuse (phase IV) and to strengthen efforts to raise awareness of the issue, more needed to be learned about the teens who were abusing dextromethorphan, their attitudes and behaviors towards abuse, and what interventions would be most effective in reaching this population. CHPA commissioned the Partnership for a Drug-Free America to conduct comprehensive research of both at-risk teens and teens and young adults who have abused or were abusing dextromethorphan.

In 2009, CHPA designed a plan to conduct additional attitudinal research into the abuser. In July and August 2010, the Partnership conducted that research with a series of focus groups of mid-teen to young-adult substance abusers. The groups took place in Baltimore, Maryland; Houston, Texas; and Los Angeles, California. Both males and females were included. In addition, Hispanics were part of the sample due to a slight increase in reported abuse by male Hispanics (PATS 2009). It is relevant to note, that no findings from the qualitative research showed that Hispanics display any unique factors that explain higher abuse prevalence than other sub-populations (Partnership 2010).

#### **Phase IV: Changing Teen Perceptions & Attitudes**

In addition to the industry's ongoing program to build parental awareness and reduce accessibility through age restrictions and restrictions on the bulk, unfinished form of the ingredient, CHPA along with the Partnership for a Drug-Free America are developing a major media intervention targeting at-risk sensation-seeking youth. This program is based on the strategy of "unselling" the cough medicine high by disseminating peer-to-peer stories and perceptions of how unpleasant the high is and how pathetic the behavior is. The objectives of this campaign are to diminish perceptions of the benefits of cough medicine abuse, increase perceptions of social disapproval of the behavior, and reduce intentions to abuse cough medicine among at-risk non-users and one or two-time users.

This approach represents a significant strengthening of industry's youth-targeted efforts to date, which have relied primarily on an online, search-driven strategy, directing young teens who are actively searching for cough medicine abuse information to the CHPA/Partnership website, DXMstories.com. (See Appendix 2.) The program moving forward will more broadly target at-risk teens by reaching not just would-be cough medicine abusers but at-risk, sensation-seeking teens. This digital campaign will have the following components:

- **A new cough medicine abuse website**, targeted to slightly older teens than the original "DXM Stories" site and featuring actual video of experienced teens either explicitly or implicitly dissuading their peers from trying dextromethorphan. The site will have viral functionality so that teen visitors can share videos and comments with their peers, expanding the reach of the prevention message. The site will be optimized not just for cough medicine abuse search terms but for all substance abuse related terms, so as to reach sensation-seeking teens as they are "researching" possible drugs to abuse, which occurs as attested to by the teen qualitative research.
- **A major marketing effort** behind the website, including digital advertising, search, video (e.g., YouTube), and social media. Again, this effort will be

targeted not to all teens but to sensation-seeking teens. The highly specialized web landscape makes it entirely possible to reach this target with precision, to avoid educating kids who are *not* at risk for the cough medicine abuse behavior.

The objective of this campaign will be to reduce the perceived benefits of cough medicine abuse, increase the perceived risks (nausea, blurred vision, and physical impairment, for example), and increase social disapproval of the behavior all with the intent of reducing initiation.

In addition to the new digital components, the program will continue to enlist parents and caregivers in the prevention effort. “Educate, communicate, and safeguard” have, to date, been the main messages of CHPA’s collective parent-targeted initiatives, delivered through a variety of channels: public service announcements, brochures, community coalitions, outreach to doctors and pharmacists, web campaigns such the Five Moms Campaign, and on package icons.

A new message, linked closely to cough medicine abuse but relevant to all parents concerned about the possibility of their child abusing drugs or alcohol, will be added. That message will educate parents about some of the risk factors that can make a child susceptible to early experimentation and substance abuse:

- A family history of addiction;
- Family traumas such as divorce or a parent’s death;
- A child’s mental health disorder such as depression or ADHD; and
- A child who is sensation-seeking, or who hangs around with friends who use drugs or drink.

### **5.3.3 Assessments of Dextromethorphan Abuse Mitigation Plan**

While the overall intent of the mitigation plan is to reduce abuse of dextromethorphan, assessments focus on changes in attitudes and perceptions about dextromethorphan abuse. CHPA has created a baseline to measure attitudes and perceptions of parents and will utilize and seek to refine existing research to measure changes in teen attitudes and perceptions. The Partnership Attitude Tracking Survey measures teen attitudes currently and has agreed to include additional questions in its ongoing survey. Additionally, the Partnership has reached out to the lead investigator for the Monitoring the Future Study, Lloyd Johnston, to ask the study team to refine the Monitoring the Future survey to include questions related to teen perceptions of risk and social approval of dextromethorphan abuse.

Certain variables make predicting a specific percentage change in abuse rates of dextromethorphan challenging:

- The self-reported abuse of dextromethorphan by teens is relatively low: five percent.
- There is uncertainty concerning the accuracy of self-reported abuse of cough medicine. Qualitative research conducted by the Partnership in 2010 suggests that teens do not understand the difference between over-the-counter cough medicine abuse and prescription cough medicine or codeine abuse leading the Partnership to believe that prescription cough medicine abuse accounts for some of the self-reported OTC cough medicine abuse.

To try to resolve this issue of how extensively prescription cough medicine abuse rates are confounding OTC cough medicine abuse prevalence data, the Partnership is working with Monitoring the Future investigators to better refine the Monitoring the Future survey by including a question on both over-the-counter cough medicine and prescription cough medicine abuse.

The assessments against which CHPA will measure the effectiveness of its interventions include some data already available as well as data the industry is working to obtain. The assessments focus on parental awareness, parental engagement (including talking with teens and monitoring medications), teen perception of risk, teen social disapproval, and the success CHPA hopes to achieve toward implementation of federal legislative initiatives to help reduce the availability of dextromethorphan to teens.

Following below are some of the baseline data currently available that will be used to help measure interventions moving forward.

**Parental awareness (David Binder Research 2010)**

2010.....46% of parents are familiar with over-the-counter cough medicine abuse

**Parent-teen conversations (PATS)**

2006(released 2007).....33% of parents talked with teens about cough & cold medicine abuse

2008 (released 2009).....65% of parents talked with teens

**Parent-teen conversations (David Binder Research 2010)**

2010.....57% of parents have talked a lot to teens about cough medicine abuse

**Parental monitoring of cough medicines (Strategy One 2008, David Binder Research 2010)**

2008.....27% of parents monitor cough medicines in the home  
2010.....31% of parents monitor cough medicines in the home

**Teen perception of risk (PATS)**

2004 (released 2005).....41%  
2009 (released 2010).....47% (sample size changed)

**Social disapproval**

*Not available | Working with Monitoring the Future to ask questions regarding social approval and perception of risk of cough medicine in future surveys*

**Passage of federal age-restriction legislation**

*Legislation introduced in the U.S. Senate in 2007 and 2009; pending before the Senate*

**Passage of federal sales prohibition of the bulk, unfinished form of dextromethorphan to non-FDA registered entities**

*Legislation passed in the U.S. House of Representatives in 2006, 2007, and 2009; current bill pending before the U.S. Senate*

**5.4 Progress To-Date on the Dextromethorphan Abuse Mitigation Plan**

CHPA and experts agree that the industry’s prevention efforts to-date are having an impact. To date, the rates of cough medicine abuse have not increased significantly and, in fact, have decreased in two age groups between 2006 and 2009 despite escalating abuse rates of some prescription drugs (Monitoring the Future). This is a fact the lead researcher of the NIDA-sponsored Monitoring the Future survey commented about in 2008 (Monitoring the Future press release 2008). It is important to note, however, that the program continues to expand based on new learning and is not fully implemented. CHPA and experts from the Partnership believe that full implementation of the interventions outlined in Section 5.3.2, education directed at teens and parents and age restrictions, will have a further impact on reducing cough medicine abuse.

## 5.5 Conclusion

CHPA, alongside and in partnership with various expert stakeholders, is engaged in ongoing and expanding interventions to address cough medicine abuse. While CHPA's interventions are still in progress and development, there is good reason to expect positive results from these efforts:

- The industry's interventions are evidenced-based and grounded in proven educational strategies with specific goals.
- Educational, parent-targeted interventions already have made some headway. Dextromethorphan abuse rates have been flat in the face of the escalating abuse rates of some prescription drugs.
- The side effects from the behavior of dextromethorphan abuse itself appears to self contain abuse.
- CHPA continues to work to understand the issue better, from its prevalence in light of possible confusion with prescription cough medicine abuse to the profile of the abuser.

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## 6. Recommendations

CHPA does not believe scheduling of dextromethorphan under the Controlled Substances Act is warranted. This conclusion is based on 50 years of marketing experience and the totality of a review of the data from pharmacology; preclinical and clinical studies related to its abuse liability; a low and flat prevalence of reported abuse from national, government-sponsored surveys; a review of outcomes databases; and dextromethorphan's benefits and risks to public health.

Instead, CHPA recommends:

- Support for expanded educational interventions
- Calling on Congress to pass legislation for a national age restriction on OTC medicines containing dextromethorphan to prohibit sale to those under age 18
- Calling on Congress to pass legislation to prohibit the sale of the unfinished, bulk form of the ingredient to any party not registered with FDA
- Calling on Congress to invest in medicine abuse programming
- Refining questions in the Monitoring the Future study and the Partnership Attitude Tracking Survey to:
  - Better track teen perceptions of risk and social approval of OTC cough medicine abuse
  - More specifically focus questions to assess dextromethorphan abuse prevalence, in contrast to OTC cough and cold medicines in general, or codeine or promethazine prescription products
- Implementing metrics to assess the impact of these plans and to guide on-going and future activities.

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## 7. References by Section

### Section 2. Regulatory Review and Market Data:

FDA 1976. Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. U.S. Department of Health and Human Services, Food and Drug Administration. Fed. Reg. 1976;41:38338–40.

FDA 1987. Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Antitussive Drug Products. U.S. Department of Health and Human Services, Food and Drug Administration. Fed. Reg. 1987;52:30042–57.

FDA 2004. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. [http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl\\_No=021620&TABLE1=OB\\_OTC](http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021620&TABLE1=OB_OTC) Accessed July 15, 2010

FDA 2008. WHO Questionnaire for Review of Dependence-Producing Psychoactive Substances by the Thirty-Fifth Expert Committee on Drug Dependence. Department of Health and Human Services (HHS). Docket ID: FDA-2008-N-0448. <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480854991> Accessed July 15, 2010

IMS, National Disease and Therapeutic Index (NDTI), July 2010.

Nielsen, The Nielson Company, 2010. Dextromethorphan Consumer Facts. Nielsen RMS and Homescan. July 2010.

Slone Epidemiology Center at Boston University, 2004. Patterns of Medication Use in the United States. A Report from the Slone Survey.

WSMI 2008. World Self-Medication Industry. OTC Ingredient Tables. <http://www.wsmi.org/otc.htm> Accessed July 15, 2010

### Section 3. Need for Access to Over-the-Counter Dextromethorphan:

AHRQ 2006. Agency for Healthcare Research and Quality. Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies. Volume 4 – Antibiotic Prescribing behavior. AHRQ Publication No. 04(06)-0051-4, January 2006.

Avalere 2009 (Bazil, M., et al.). Managing Access to Pseudoephedrine. Stakeholder Impacts of a Prescription-Only Policy. September 2009.

Barrett, B., Brown, R., Mundt, M., et al., 2005. The Wisconsin Upper Respiratory Symptom Survey is responsive, reliable, and valid. *Journal of Clinical Epidemiology* 58, 609–617.

Boyd, E.M., Boyd, C.E., 1960. Chlophedianol hydrochloride: a new antitussive agent. *Canad. M. A. J.* 83, 1298-1301.

Bramley, T.J., Lerner, D., Sarnes, M., 2002. Productivity Losses Related to the Common Cold. *J. Occup. Environ. Med.* 44, 822–829.

Brignall, K., Jayaraman, B., Birring, S., 2008. Quality of Life and Psychosocial Aspects of Cough. *Lung* 186 (Suppl 1), 55-58.

CESAR, 2007. Drug information: DXM.

CDC 2010. Centers for Disease Control and Prevention (CDC). Seasonal Influenza. April 26, 2010. <http://www.cdc.gov/flu/about/qa/disease.htm> Accessed July 15, 2010

Cherry, D.K., Hing, E., Woodwell, D.A., Rechtsteiner, E.A., 2008. National Ambulatory Medical Care Survey: 2006 Summary. *National Health Statistics Reports*, Number 3, August 6, 2008.

Cornford, C.S., 1998. Why patients consult when they cough: a comparison of consulting and non-consulting patients. *Br J Gen Pract.* 48, 1751-1754.

Curley, F.J., Irwin, R.S., Pratter, M.R., et al., 1988. Cough and the common cold. *Am. Rev. Respir. Dis.* 138, 305-311.

DeLancey, J.O.L., 2010. Why Do Women have Stress Urinary Incontinence? *Neurourology and Urodynamics* 29, S13–S17.

Eccles, R., 2005. Understanding the symptoms of the common cold and influenza. *Lancet Infect. Dis.* 5, 718–725.

Eccles, R., 2009. Over the counter medicines for colds. In: Eccles, R., Weber, O. (ed.). *Common Cold*. 2009 Birkhäuser Verlag Basel/Switzerland (pp. 249-273).

Fendrick, A.M., Monto, A.S., Nightengale, B., Sarnes, M., 2003. The economic burden of non-influenza-related viral respiratory tract infection in the United States. *Arch. Intern. Med.* 163, 487-494.

French, C.T., Irwin, R.S., Fletcher, K.E., Adams, T.M., 2002. Evaluation of a Cough-Specific Quality-of-Life Questionnaire. *Chest* 121, 1123-1131.

French, C.T., Irwin, R.S., Fletcher, K.E., 2005. A Comparison of Gender Differences in Health-Related Quality of Life in Acute and Chronic Coughers. *Chest* 127, 1991-1998.

GAO 1995. United States General Accounting Office. Nonprescription drugs. Value of a pharmacist-controlled class has yet to be determined. August 1995.

Hendley, J.O., Gwaltney, J.M., 1988. Mechanisms of transmission of rhinovirus infections. *Epidemiologic Reviews* 10, 242-258.

Hueston, W.J., Mainous, A.G., Ornstein, S., Pan, Q., Jenkins, R., 1999. Antibiotics for Upper Respiratory Tract Infections. Follow-up Utilization and Antibiotic Use. *Arch. Fam. Med.* 8, 426-430.

Irwin, R.S., French, C.T., Fletcher, K.E., 2002. Quality of Life in Coughers. *Pulmonary Pharmacology & Therapeutics* 15, 283-286.

Irwin, R.S., 2006. Introduction to the diagnosis and management of cough. *Chest* 129 (Suppl), 25S-27S.

Janson, C., Chinn, S., Burney, P., 2001. Determinants of cough in young adults participating in the European Community Respiratory Health Survey. *Eur. Respir. J.* 18, 647-654.

Metlay, J.P., Stafford, R.S., Singer, D.E., 1998. National Trends in the Use of Antibiotics by Primary Care Physicians for Adult Patients With Cough. *Arch. Intern. Med.* 158, 1813-1818.

Michaels Opinion Research 2007. Key findings of a national survey on cough medicine use. Consumer Healthcare Products Association (CHPA). January 26, 2007.  
[http://www.chpa-info.org/media/resources/r\\_4510.pdf](http://www.chpa-info.org/media/resources/r_4510.pdf) Accessed July 15, 2010.

NCPIE 2008. National Council on Patient Information and Education (NCPIE). Self-medication and Allergies Survey. January 2008. <http://www.bemedwise.org/survey/ExecutiveSummary.pdf>  
Accessed July 15, 2010.

NIAID 2007. National Institute of Allergy and Infectious Diseases (NIAID). December 06, 2007  
<http://www.niaid.nih.gov/topics/commonCold/Pages/overview.aspx> Accessed July 15, 2010.

Pisu, M., Meltzer, M.I., Hurwitz, E.S., Haber, M., 2005. Household-based costs and benefits of vaccinating healthy children in daycare against influenza virus. Results from a primary study. *Pharmacoeconomics*. 23, 55-67.

Prosser, L.A., O'Brien, M.A., Molinari, N.A.M., et al., 2008. Non-traditional settings for influenza vaccination of adults. Costs and cost effectiveness. *Pharmacoeconomics* 26, 163-178.

Rohde, G., 2009. Drug targets in rhinoviral infections. *Infect. Disord. Drug Targets* 9, 126-132.

Swanson, J.G., Kaczorowski, J., Skelly, J., Finkelstein, M., 2005. Urinary incontinence. Common problem among women over 45. *Can. Fam. Physician* 51, 84-85.

Tang, J.W., Li, Y., Eames, I., Chan, P.K.S., Ridgway, G.L., 2006. Factors involved in the aerosol transmission of infection and control of ventilation in healthcare premises. *Journal of Hospital Infection* 64,100-114.

Tang, J.W., Liebner, T.J., Craven, B.A., Settles, G.S., 2009a. A schlieren optical study of the human cough with and without wearing masks for aerosol infection control. *J. R. Soc. Interface* 6 (Suppl 6), S727-736.

Tang, J.W., Settles, G., 2009b. Coughing and masking. *NEJM* 361, 26.

Tang, J.W., 2010. Estimation of number of influenza viruses expelled by cough. Personal communication. July 2010.

Vernon, M., Kline Leidy, N., Nacson, A., Nelsen, L., 2009. Measuring cough severity: Perspectives from the literature and from patients with chronic cough. *Cough* 5: 5.

Yousaf, N., Jayaraman, B., Pavord, I.D., Birring, S.S., 2009. Acute Cough: measurement of QoL with the Leicester Cough Questionnaire (LCQ). *Thorax* 64, P175.

#### **Section 4. Analysis of Abuse Potential:**

American Medical Association, December 2004. Report of Council on Scientific Affairs: Dextromethorphan abuse. *Scientific Affairs* – 1, 269.

Aylward, M., Maddock, J., Davies, D.E., Protheroe, D.A., Leideman, T., 1984. Dextromethorphan and codeine: comparison of plasma kinetics and antitussive effects. *Eur. J. Resp. Dis.* 65, 283–91.

Barrett, R.L., Wiley, J.L., Balster, R.L., Martin, B.R., 1995. Pharmacological specificity of tetrahydrocannabinol discrimination in rats. *Psychopharm.* 118, 419-424.

Bem, J.L., Peck, R., 1992. Dextromethorphan: An overview of safety issues. *Drug Safety* 7, 190-199.

Bobelis, D.J., Balster, R.L., 1993. Pharmacological specificity of the discriminative stimulus properties of 2-amino-4,4-(1,2-cyclohexyl)-7-phosphono-heptanoic acid (NPC 12626), a competitive N-methyl-D-aspartate receptor antagonist. *J. Pharm. And Exper. Therp.* 264, 845-853.

Bolser, D.C., Hey, J.A., Chapman, R.W., 1999. Influence of central antitussive drugs on the cough motor pattern. *J. Appl. Physiol.* 86,1017–1024.

Buch, S., Kotekar, A., Kawle, D., Bhisey, R., 2001. Polymorphisms at CYP and GST gene loci. Prevalence in the Indian population. *Eur. J. Clin. Pharmacol.* 57, 553-555.

Cai, W.M., Chen, B., Liu, Y.X., Chu, X., 1997. Dextromethorphan metabolic phenotyping in a Chinese population. *Acta Pharmacologica Sinica* 18, 441-444.

Canning B.J., 2009. Central Regulation of the Cough Reflex: Therapeutic Implications. *Pulm. Pharmacol. Ther.* 2009 April; 22(2): 75–81.

Capon, A., Bochner, F., Kerry, N., et al., 1996. The influence of CYP2D6 polymorphism and quinidine on the disposition and antitussive effect of dextromethorphan in humans. *Clin. Pharmacol. Ther.* 60, 295-307.

Casner, P.R., 2005. The Effect of CYP2D6 Polymorphisms on Dextromethorphan Metabolism in Mexican Americans. *J. Clin. Pharmacol.* 45; 1230-1235.

Chyka, P.A., Erdman, A.R., Manoguerra, A.S., et al., 2007. Dextromethorphan poisoning: An evidence-based consensus guideline for out-of-hospital management. *Clin. Tox.* 45, 662-677.

Cone, E.J., 2006. Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the internet. *Drug and Alcohol Dependence.* 83S, S31-S39.

Cranston, J.W., Yoast, R., 1999. Abuse of dextromethorphan. *Arch. Fam. Med.* 8, 99-100.

DEA 2009. Drug Enforcement Administration, National Forensic Laboratory Information System. Annual and semi-annual reports. Analysis on file, Pinney Associates, 2010.

Evans, W.E, Relling, M.V., Rahman, A., et al., 1993. Genetic Basis for a Lower Prevalence of Deficient CYP2D6 Oxidative Drug Metabolism Phenotypes in Black Americans. *J. Clin. Invest.* 91, 2150-2154.

FDA 1976. Food and Drug Administration. Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. U.S. Department of Health and Human Services, Food and Drug Administration. *Fed. Reg.* 1976; 41, 38338–40.

FDA 2009. Food and Drug Administration. General Drug Categories. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm176533.htm> Accessed July 15, 2010

FDA 2010. Food and Drug Administration. Guidance for Industry. Assessment of Abuse Potential of Drugs. Draft Guidance. January 2010.

Fossati, A., Vimercati, M.G., Caputo, R., Valenti, M., 1995. Pharmacological profile of dextrophan. *Arzneimittelforschung* 45, 1188-1193.

France, C.P., Moerschbaeche, J.M., Woods, J.H., 1991. Erratum: MK-801 and related compounds in monkeys: Discriminative stimulus effects and effects on a conditional discrimination. *J. Pharm. And Exper. Therap.* 257, 727-733.

- Fuller R.W., Haase G., Choudry, N.B., 1989. The effects of dextromethorphan cough syrup on capsaicin-induced cough in normal volunteers. *Am. Rev. Respir. Dis.* 139. A11.
- Gavend, M., Mallaret, M., Dematteis, M., Baragatti, G., 1995. Discriminative stimulus properties of dextromethorphan in rats. *Biomed. & Pharmacother.* 49, 456-464.
- Grattan, T. J., Marshall, A. E., Higgins, K. S., Morice, A. H., 1995. The effect of inhaled and oral dextromethorphan on citric-acid induced cough in man. *Br. J. Clin. Pharmacol.* 39, 261-263.
- Griffiths, R.R., Bigelow, G.E, Ator, N.A, 2003. Principles of initial experimental drug abuse liability assessment in humans. *Drug and Alcohol Dependence* 70. S41-S54.
- He, N., Daniel, H.I., Hajiloo, L., Shockley, D., 1999. Dextromethorphan O-demethylation polymorphism in an African-American population. *Eur. J. Clin. Pharmacol.* 55, 457-459.
- Holtzman, S.G., 1982. Phencyclidine-like discriminative stimulus properties of opioids in the squirrel monkey. *Psychopharm.* 77, 295-300.
- Holtzman, S.G., 1994. Discriminative stimulus effects of dextromethorphan in the rat. *Psychopharm.* 116, 249-254.
- Jasinski, D.R., Martin, W.R., Mansky, P.A., 1971. Progress report on the assessment of the antagonists nalbuphine and GBA-2087 for abuse potential and studies of the effects of dextromethorphan in man. Reported to the 33rd Annual Scientific Meeting, Committee on Problems of Drug Dependence. National Research Council, Washington, DC. pp. 143-178.
- Jasinski, D.R., 2000. Abuse Potential of Morphine/Dextromethorphan Combinations. *Journal of Pain and Symptom Management* 19 (No.1, Suppl. 1), 26-30.
- Jun, J.H., Thorndike, E.B., Schindler, C.W., 2004. Abuse liability and stimulant properties of dextromethorphan and diphenhydramine combinations in rats. *Psychopharm.* 172, 277-282.
- Karttunen, P., Silvasti, M., Virta, P., Saano, V., Nuutinen, J., 1990. The Effects of Vadocaine, Dextromethorphan, Diphenhydramine and Hydroxyzine on the Ciliary Beat Frequency in Rats *in Vitro*. *Pharmacology & Toxicology* 67, 159-161.
- Kotzer, C.J., Hay, D.W., Dondio, G., Giardina, G., Petrillo, P., Underwood, D.C., 2000. The antitussive activity of delta-opioid receptor stimulation in guinea pigs. *J. Pharmacol. Exp. Ther.* 292, 803-809.
- Lipsky, M.S., et al., 2004. An economic analysis for treating viral upper respiratory tract infection in the United States. Presentation on file, CHPA.
- Michaels Opinion Research 2007. Key findings of a national survey on cough medicine use. Consumer Healthcare Products Association (CHPA). January 26, 2007.

Miller, S.C., 2005. Dextromethorphan psychosis, dependence and physical withdrawal. *Addiction Biology* 10, 325-327.

Mori, A., Noda, Y., Mamiya, T., Miyamoto, Y., Nakajima, A., Furukawa, H., Nabeshima, T., 2001. Phencyclidine-induced discriminative stimulus is mediated via phencyclidine binding sites on the N-methyl-D-aspartate receptor-ion channel complex, not via sigma receptors. *Behav. Brain Research* 119, 33-40.

MTF 2006. Institute for Social Research, University of Michigan, Monitoring the Future survey, 2006.

MTF 2007. Institute for Social Research, University of Michigan, Monitoring the Future survey, 2007.

MTF 2008. Institute for Social Research, University of Michigan, Monitoring the Future survey, 2008.

MTF 2009. Institute for Social Research, University of Michigan, Monitoring the Future survey, 2009.

Nagai, N., Kawakubo, K., Kanekoi, F., et al., 1996. Pharmacokinetics and polymorphic oxidation of dextromethorphan in a Japanese population. *Biopharmaceutics & Drug Disposition* 17, 421-433.

Narita, M., Yoshizawa, K., Nomura, M., Aoki, K., Suzuki, T., 2001. Role of the NMDA receptor subunit in the expression of the discriminative stimulus effect induced by ketamine. *European J. Pharm.* 423, 41-46.

Nicholson, K.L., Hayes, B.A., Balster, R.L., 1999. Evaluation of the reinforcing properties and phencyclidine-like discriminative stimulus effects of dextromethorphan and dextrorphan in rats and rhesus monkeys. *Psychopharm.* 146, 49-59.

NSDUH 2008. Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Results from the 2008 National Survey on Drug Use and Health: National Findings, September 10, 2009

Overton, D.A., Batta, S.K., 1979. Investigation of narcotics and antitussives using drug discrimination techniques. *J. Pharm. And Exper. Therap.* 211,401-408.

Pavesi, L., Subburaj, S., Porter-Shaw, K., 2001. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough. *Chest* 120, 1121-1128.

Pinney Associates, Internet monitoring analysis, on file, CHPA, 2010.

Ramsay, J., Wright, C., Thompson, R., Hull, D., Morice, A.H., 2008. Assessment of antitussive efficacy of dextromethorphan in smoking related cough: objective vs. subjective measures. Br. J. Clin. Pharmacol. 65, 737-41.

SAMHSA 2006. Office of Applied Studies, Substance Abuse and Mental Health Services Administration, The new DAWN report: Emergency department visits involving dextromethorphan, issue 32, 2006.

SAMHSA 2009. Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS). Data received through August 31, 2009. Analysis on file, Pinney Associates.

SAMHSA 2010. Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Drug Abuse Warning Network (DAWN). Drug misuse and abuse visits. Accessed August 14, 2010.

Schadel, M., Wu, D., Otton, S.V., Kalow, W., Sellers, E.M., 1995. Pharmacokinetics of dextromethorphan and metabolites in humans: Influence of the CYP2D6 phenotype and quinidine inhibition. *J. Clin. Psychopharm.* 15, 263-269.

Schwartz, R.H., 2005. Adolescent abuse of dextromethorphan. *Clin. Pediatr.* 44, 565-568.

Silvasti, M., Karttunen, P., Tukiainen, H., Kokkonen, P., Hanninen, U., Nykanen, S., 1987. Pharmacokinetics of dextromethorphan and dextrophan: A single dose comparison of three preparations in human volunteers. *International J. Clin. Pharm., Ther. & Tox.* 25, 493-487.

Siu, A., Drachtman, R., 2007. Dextromethorphan: A review of N-methyl-D-aspartate receptor antagonist in the management of pain. *CNS Drug Reviews* 13, 96-106.

Soyka, M., Bondy, B., Eisenburg, B., Schütz, C.G., 2000. NMDA receptor challenge with dextromethorphan – subjective response, neuroendocrinological findings and possible clinical implication. *J. Neural Transm.* 107, 701-714.

Takashima, T., Murase, S., Iwasaki, K., Shimada, K., 2005. Evaluation of dextromethorphan metabolism using hepatocytes from CYP2D6 poor and extensive metabolizers. *Drug Metab. Pharmacokinet.* 20, 177-182.

USDOJ/DEA 2010. U.S. Department of Justice, Drug Enforcement Administration. Dextromethorphan.  
[http://www.deadiversion.usdoj.gov/drugs\\_concern/dextro\\_m/dextro\\_m.htm](http://www.deadiversion.usdoj.gov/drugs_concern/dextro_m/dextro_m.htm)  
Accessed July 15, 2010

Veticaden, S.J., Cabana, B.E., Prasad, V.K, et al., 1989 Phenotypic Differences in Dextromethorphan Metabolism. *Pharmaceutical Research* 6, 13-19.

Winger, G., Herling, S., 1982. Discriminative stimulus effects of pentobarbital in rhesus monkeys: Tests of stimulus generalization and duration of action. *Psychopharm.* 76, 172-176.

Wright Jr., M.J., Vann, R.E., Gamage, T.F., Damaj, M.I., Wiley, J.L., 2006. Comparative effects of dextromethorphan and dextrorphan on nicotine discrimination in rats. *Pharmacol. Biochem. Behav.* 85, 507-513.

Zakharova, E.S., Danysz, W., Bespalov, A.Y., 2005. Drug discrimination analysis of NMDA receptor channel blockers as nicotinic receptor antagonist in rats. *Psychopharm.* 179, 128-135.

Zawertailo, L.A., Tyndale, R.F., Busto, U., Sellers, E.M., 2010. Effect of metabolic blockade on the psychoactive effects of dextromethorphan. *Human Psychopharm.* 25, 71-79.

### **Section 5. Reducing Dextromethorphan Abuse Through Evidence-Based Interventions:**

David Binder Research, 2010. Survey of 800 U.S. parents of children between 12-18 on OTC cough medicine abuse attitudes and reported behaviors. On file, CHPA, 2010.

DAWN. Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Drug Abuse Warning Network (DAWN). Drug misuse and abuse visits. Accessed August 14, 2010.

Delaney, B., 2003. Adolescent Risk Behavior Research and Media-Based Health Messages. In Romer, D. (ed.). *Reducing Adolescent Risk: Toward an Integrated Approach*. Sage Publications, Inc., 203-209.

Griffin, K. W., 2003. Contemporary School-Based Prevention Approaches and the Perceived Risks and Benefits of Substance Use. In Romer, D. (ed.). *Reducing Adolescent Risk: Toward an Integrated Approach*. Sage Publications, Inc., 93-98.

Johnston, L.D., 2003. Alcohol and Illicit Drugs: The Role of Risk Perceptions. In Romer, D. (ed.). *Reducing Adolescent Risk: Toward an Integrated Approach*. Sage Publications, Inc., 56-74.

MTF 2006. Institute for Social Research, University of Michigan, Monitoring the Future survey, 2006.

MTF 2007. Institute for Social Research, University of Michigan, Monitoring the Future survey, 2007.

MTF 2008. Institute for Social Research, University of Michigan, Monitoring the Future survey, 2008.

MTF 2009. Institute for Social Research, University of Michigan, Monitoring the Future survey, 2009.

MTF 2008. Institute for Social Research, University of Michigan, Monitoring the Future press release, December 11, 2008. Available at [monitoringthefuture.org/pressreleases/08drugpr\\_complete.pdf](http://monitoringthefuture.org/pressreleases/08drugpr_complete.pdf).

National Institute on Alcohol Abuse and Alcoholism, 2008. U.S. Fatality Analysis Reporting System. Trends in alcohol related and non alcohol related traffic fatalities, persons ages 16-20, U.S., 1982-

2006. <http://www.madd.org/parents/parents/research/view-research.aspx?research=22>. Accessed August 10, 2010.

NSDUH 2008. Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Results from the 2008 National Survey on Drug Use and Health: National Findings, September 10, 2009

Partnership for a Drug-Free America qualitative research on OTC cough medicine abuse attitudes among teens and young adults. On file, CHPA, 2010.

Partnership for a Drug-Free America qualitative research on OTC cough medicine abuse attitudes among parents. Personal communication, CHPA, 2005.

PATS 2009. Partnership for a Drug-Free America, MetLife Foundation, Partnership Attitude Tracking Study (PATS), 2009.

PATS 2009. Partnership for a Drug-Free America, The Partnership Attitude Tracking Study (PATS): Parents with Children in Grades 7-12, 2006.

Pinney Associates, Internet monitoring analysis. On file, 2010.

Strategy One, quantitative survey. On file, CHPA 2008.

Romer 2003. See Delaney, Griffin, and Johnston citations.

TEDS. Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS). Data received through August 31, 2009. Analysis on file, Pinney Associates.

U.S. v. Johnson (S.D. Ind.), January 10, 2006, as reported in FDA Inspections, Compliance, Enforcement, and Criminal Investigations Court Updates and Litigations Summaries, fiscal year 2006.

Zawertailo, L.A., Tyndale, R.F., Busto, U., Sellers, E.M., 2010. Effect of metabolic blockade on the psychoactive effects of dextromethorphan. *Human Psychopharm.* 25, 71-79.