



founded 1881

October 20, 2008

Division of Dockets Management
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; ... Dextromethorphan ..., 73 Fed. Reg. 51823 (September 5, 2008) [Docket No. FDA-2008-N-0448]

Dear Sir or Madam:

On September 5, 2008, the Food and Drug Administration (FDA) published the above-referenced notice requesting comments concerning abuse potential, actual abuse, medical usefulness, trafficking, and impact of scheduling changes on availability for medical use of 10 drug substances as the U.S. Government prepares a response to a World Health Organization (WHO) notification on the subject.

The Consumer Healthcare Products Association (CHPA), founded in 1881, is the national trade association representing manufacturers and distributors of over-the-counter (OTC), or nonprescription medicines, and dietary supplements in the United States, including OTC cough suppressants containing dextromethorphan. Dextromethorphan, the most commonly used OTC cough suppressing ingredient in the U.S., is one of the 10 drug substances included in FDA's notice. CHPA members account for over 90 percent of the domestic retail sales of OTC medicines, including cough suppressants. As such, we have an interest in the subject matter of the notice.

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Dextromethorphan is a safe, effective cough suppressant which has been found generally recognized as safe and effective by FDA.¹ In fact, dextromethorphan is a safe, effective cough suppressant used in many countries around the world, with a history of use of over 50 years.²

As discussed in these comments, there is insufficient evidence that dextromethorphan is being abused so as to constitute a public health and social problem warranting the placing of dextromethorphan under international control; nor does it have dependence-producing capacity as is needed for United Nations Convention on Psychotropic Substances scheduling. The types of controls envisioned under the UN Convention on Psychotropic Substances are not merited for dextromethorphan. Further, such controls would run counter to existing U.S. policies.

If dextromethorphan nevertheless **were** to be subject to international scheduling, it would come at a great cost to citizens who use this safe, effective medicine to treat their coughs.

We urge the U.S. Government to recommend to the WHO and its Expert Committee on Drug Dependence that dextromethorphan not move forward for further action after the April 2009 pre-review.

The agency's *Federal Register* notice included a series of question areas taken from the WHO notification, which we address in turn.

1. Legitimate use of the substance

As FDA's notice points out, dextromethorphan is currently authorized as a medical product in the U.S. Dextromethorphan is a generally recognized as safe and effective oral antitussive for the treatment of coughs. It has been available in the U.S. for over 50 years.³ It is marketed in the U.S. without a prescription in liquid and solid dosage forms in both single ingredient and multi-symptom relief medicines. The OTC dose for adults is 10 to 20 mg, every 4 hours; or 30 mg every 6-8 hours; not to exceed 120 mg in 24 hours, or as directed by a doctor.⁴ The ingredient is also available in an OTC medicine under a new drug application in an oral suspension combination with guaifenesin in a 60 mg extended release dose.⁵

¹ See 21 CFR 341.14.

² According to a survey updated annually by CHPA's equivalent association in Europe, the Association of the European Self-Medication Industry (AESGP), as of February 2007, 29 of the 36 industry country associations responding to the survey indicated the ingredient was available without a prescription; 4 indicated it was available as a prescription medicine; 2 indicated it was not registered in their country; and 1 additional association indicated it was available without a prescription but we cannot verify the information. See Smith, "Dextromethorphan/quinidine," *Expert Opin. Pharmacother.* 7: 2581 (2006), noting use in the U.S. since 1958.

³ See Smith, *supra*. Studies submitted for the antitussive portion of FDA's OTC Review cough, cold, allergy, bronchodilator and antiasthmatic products monograph date to 1953. 41 Fed. Reg. 38312, 38340 (September 9, 1976).

⁴ See 21 CFR 341.74.

⁵ See <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

While CHPA represents manufacturers of nonprescription medicines, we also note that FDA's web site observes that the ingredient is included with the prescription ingredient promethazine in combination prescription medicines as well.⁶

Research has been conducted with dextromethorphan for a number of neurological disorders, but there are no approved uses of the ingredient in the U.S. other than as an oral antitussive.⁷

Dextromethorphan is included in a number of widely available OTC medicine brands in the U.S., either as the only active ingredient or in combination with other active ingredients, including Alka-Seltzer Plus Cold & Cough Formula, Coricidin HBP Cough and Cold, some Delsym products, Dimetapp DM, Hold DM, some Mucinex products, PediaCare cough medicines, certain Robitussin cough products, Sudafed cough products, TheraFlu Cough products, Triaminic cough products, Tylenol Cough and Tylenol Cold products, Vicks 44 Cough Relief products, certain Vicks DayQuil and NyQuil LiquiCaps, Zicam, and store brand equivalents.

We are not aware of any technical uses of dextromethorphan.

The basic safety and effectiveness of dextromethorphan were demonstrated through submissions during the development of the antitussive portion of FDA's cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter human use monograph in the OTC Review.⁸ The review by the FDA advisory panel included a large number of clinical studies conducted with dextromethorphan over the previous 20 years. These comprised trials with experimentally induced cough, controlled studies in pathologic cough with both subjective and objective efficacy endpoints, and uncontrolled studies in a variety of disease states. Most of these clinical studies showed that dextromethorphan was superior to placebo. Since the final monograph was published, various investigators have continued to conduct clinical studies with dextromethorphan. More recently, two placebo-controlled clinical studies in induced cough models have been published, one by Karttunen *et al.*⁹ and the other by Abdul Manap *et al.*¹⁰. In 1996, Parvez *et al.* reported the results of three placebo-controlled studies (n=108, 134, 209) with a single 30 mg dose of dextromethorphan for acute cough due to acute upper respiratory infection¹¹. With the exception of a study with a smaller sample size (n=43) by Lee *et al.*

⁶ Id., including Drugs@FDA prescription drug listings for Bromfed-DM, Myphetane DX, promethazine with dextromethorphan, promethazine DM, promethazine hydrochloride and dextromethorphan hydrobromide, and promethazine with dextromethorphan.

⁷ See Smith, *supra*, describing studies on dextromethorphan in neurological conditions.

⁸ See 41 Fed. Reg. 38312, 38340 (September 9, 1976), for the FDA OTC Review advisory panel report on dextromethorphan. Label requirements for the ingredient were later codified in 21 CFR 341.

⁹ Karttunen P, Tukiainen H, Silvasti M, Kolonen S: Antitussive Effect of dextromethorphan and Dextromethorphan-Salbutamol Combination in Healthy Volunteers with Artificially Induced Cough. *Respiration* 1987, 52(1):49-53.

¹⁰ Abdul Manap R, Wright CE, Gregory A, Rostami-Hodjegan A, Meller ST, Kelm GR, Lennard MS, Tucker GT, Morice AH: The antitussive effect of dextromethorphan in relation to CYP2D6 activity. *Br J Clin Pharmacol* 1999, 48(3):382-387.

¹¹ Parvez L, Vaidya M, Sakhardande A, Subburaj S, Rajagopalan TG: Evaluation of Antitussive Agents in Man. *Pulm Pharmacol* 1996, 9(5-6):299-308.

published in 2000¹² these newer studies showed statistically significant superior efficacy for dextromethorphan over placebo as determined by objective cough measurements and subjective visual analog scales. In 2001, Pavesi *et al.* conducted a meta-analysis of efficacy studies with a single 30 mg dose of dextromethorphan in acute cough due to acute upper respiratory infection¹³. This meta-analysis of six placebo-controlled clinical studies which all used objective cough recording showed significantly greater increases in cough latency (on average +17.3%) and significantly greater reductions in cough bouts (-12.7%), cough components (-13.4%), and cough effort (-17.3%) for dextromethorphan compared to placebo. According to the guideline on cough assessment recently published by the European Respiratory Society (ERS), any parallel group study in acute cough must include large patient numbers to detect an effect because of the natural individual variability in cough frequency across measurement times, the variability in response to medication, and the significant placebo effect. The ERS task force further expressed the opinion that the meta-analysis by Pavesi *et al.*, which considered results from more than 700 patients, was a robust analysis demonstrating antitussive efficacy¹⁴.

A recent open-label study found 92 percent of study subjects using dextromethorphan experienced excellent, very good, or good relief of their cough symptoms, with 90 percent reporting they were satisfied with the medication.¹⁵

The ingredient's usefulness in the everyday lives of Americans and citizens of other countries is underscored by the prevalence of coughs: 41 percent of adults nationwide experienced a cough in the past three months, according to a survey conducted in January 2007. Among households with children under the age of 18, the reported incidence of a child in the home experiencing a cough in the past three months is even higher at 56 percent. The overwhelming majority of Americans who experienced a cough took active steps to treat their symptoms or discomfort, with approximately two-thirds of adults treating the cough with an OTC cough medicine, and 73 percent of parents and caregivers administering an OTC cough medicine to the child in their home who was experiencing a cough.¹⁶ Using the more conservative adult percentages, that translates to an estimated 81 million people in the U.S. therapeutically using a safe, effective cough medicine in a three-month timeframe.¹⁷

It is equally important to note that 96 percent of American adults who used an OTC cough medicine to treat a cough they or a child in their household was experiencing report the

¹² Lee PCL, Jawad MSM, Eccles R: Antitussive Efficacy of Dextromethorphan in Cough Associated with Acute Upper Respiratory Tract Infection. *J Pharm Pharmacol* 2000, 52:1137-1142.

¹³ Pavesi L, Subburaj S, Porter-Shaw K: Application and Validation of a Computerized Cough Acquisition System for Objective Monitoring of Acute Cough: A Meta-analysis. *Chest* 2001, 120 (4):1121-1128.

¹⁴ Morice AH, Fontana GA, Belvisi MG, Birring SS, Chung KF, Dispinigaitis PV, Kastelik JA, McGarvey LP, Smith JA, Tatar M, Widdicombe J: ERS guidelines on the assessment of cough. *Eur Respir J* 2007, 29 (6):1256-1276.

¹⁵ M. Howard, et al., "Evaluation of users' perceptions of effectiveness and satisfaction with an OTC cough suppressant: a multi-center open-label study," manuscript on file at CHPA; submitted for publication.

¹⁶ "Key Findings of a National Survey on Cough Medicine Use," Michaels Opinion Research for CHPA, January 26, 2007.

¹⁷ The annual estimate for the population of the United States for July 2007 was 301,621,157 people. See <http://www.census.gov/popest/estimates.php>.

medicine was helpful. Adults in the survey reported that the medicine provided at least one form of relief, such as helping them cough less or feel more comfortable.¹⁸

Last as to legitimate use, the WHO questionnaire asks about the sources of dextromethorphan. A wide number of countries are among the sources of dextromethorphan as an active pharmaceutical ingredient, including India, Switzerland, Germany, the U.S., and others, which is manufactured into finished dosage forms both domestically and internationally.

2. Abuse of the substance

Unfortunately, there are reports of dextromethorphan being taken in large quantities – well beyond the appropriate medical dose, even 25 or more times the dose. Intentional abuse usually involves finished products which are swallowed directly for inappropriate purposes, as opposed to first extracting and then ingesting or otherwise administering the ingredient.¹⁹ The web site www.erowid.com, which describes itself as providing “non-judgmental information about psychoactive plants and chemicals and related issues,” similarly describes use of dextromethorphan-containing finished products. These cases of reported intentional abuse frequently include use of alcohol or other substances.²⁰ There is one published case report of dextromethorphan being extracted from finished products.²¹ This appears to be an isolated occurrence.

Inappropriate use of dextromethorphan in the U.S. is largely focused in teenagers.²² The 2006 National Survey on Drug Use and Health by the Substance Abuse and Mental Health Administration (SAMHSA), found 5.3 percent of respondents aged 12 to 25 reported having ever used an OTC cough medicine to seek to get “high”, with 1.7 percent reporting having done so in the past year.²³ For respondents aged 12-17, the figure for trial in the past year was 1.9 percent, contrasted with 1.6 percent for respondents aged 18-25.²⁴

Data from the National Institute on Drug Abuse’s (NIDA’s) 2007 Monitoring the Future survey found higher results than the 2006 SAMSHA survey, with 4.0 percent of eighth graders, 5.4 percent of 10th graders, and 5.8 percent of 12th graders responding affirmatively to a question on use of OTC cough medicine over the past year to “get high”.²⁵ Because this question was first introduced in the 2006 Monitoring the Future study, which found similar results, we cannot yet analyze teen-reported survey trends over time. By contrast to the OTC cough

¹⁸ Michaels Opinion Research, *supra*.

¹⁹ Hendrickson, et al, “Abstract: Crystal Dex -- Purified DXM Using an Acid/Base Extraction,” *Journal of Toxicology, Clinical Toxicology*, 42: 757 (2004).

²⁰ See Lessenger, et al., “Abuse of Prescription and Over-the-Counter Medications,” *Journal of the American Board of Family Medicine*, 21: 45 (2008), citing Drug Abuse Warning Network data that people who abuse prescription or OTC medications tend to mix their medications with alcohol. See also subsequent discussion of DAWN reports.

²¹ Hendrickson, *supra*.

²² Boyer, “Dextromethorphan Abuse,” *Pediatric Emergency Care*, 20: 858 (2004).

²³ “Misuse of Over-the-Counter Cough and Cold Medications among Persons Aged 12 to 25,” *The National Survey on Drug Use and Health Report*, January 10, 2008.

²⁴ *Id.*

²⁵ “Monitoring the Future,” University of Michigan for National Institute of Drug Abuse, 2007, available through <http://www.drugabuse.gov/DrugPages/MTF.html>

medicine question, 9.6 percent of 12th graders report using Vicodin within the past year “on your own – that is, without a doctor telling you to take [it]”.²⁶

A report for the Utah Department of Human Services shows the drop-off of intentional abuse by the time individuals reach college age. In a survey of over 10,000 college students to determine the prevalence of intentional substance abuse on Utah’s college campus, the survey found 99.3 percent of college students reported zero occasions of using dextromethorphan to get high in the past year versus 0.7 percent of respondents who reported dextromethorphan use to get high in the past year.²⁷

In light of these survey results, it becomes even more important to examine the public health impact of reported intentional abuse.

As reported in SAMSHA’s Drug Abuse Warning Network (DAWN) data, for calendar year 2004, emergency department visits involving dextromethorphan made up 0.7 percent – roughly one in every 140 – of all drug-related emergency department visits.²⁸ By comparison, 13.5 percent of all drug-related emergency department visits came from prescription opiates/opioids for 2005, according to DAWN estimates.²⁹ While these figures were drawn from different years, consider that the Rx opiate/opioid percentage is on the order of 20 times higher against the fact that an estimated 81 million people in the U.S. are therapeutically using a safe, effective OTC cough medicine in a three-month timeframe.³⁰

The DAWN report indicates that nearly half of emergency department visits resulting from “nonmedical use” of dextromethorphan are in the 12-20 age group, which is consistent with findings that intentional abuse is focused in teenagers.³¹ Emergency department visits per 100,000 fall from 7.1 for this age group to 2.6 per 100,000 among those 21-34.³² By inference, this also speaks to a low risk of physical or psychological dependence on dextromethorphan. It is known that overall emergency department visits for the “nonmedical use” of **any** pharmaceutical is higher among those 21-34 than it is for those age 12-20.³³

²⁶ Id.

²⁷ Harrison, “Utah Higher Education Health Behavior: Final Report 2007,” for the Utah Division of Substance Abuse and Mental Health, October 2007.

²⁸ “Emergency Department Visits Involving Dextromethorphan,” The New DAWN Report, Office of Applied Studies, SAMSHA, issue 32, 2006.

²⁹ See “Drug Abuse Warning Network, 2005: National Estimates of Drug-Related Emergency Department Visits,” Office of Applied Studies, SAMSHA, February 2007 (196,225 estimated visits of nonmedical use of prescription opiates/opioids out of an estimated 1.449 million emergency department visits).

³⁰ Michaels Opinion Research, *supra*, note 11. Six multinational companies represented by CHPA, comprising a majority of OTC medicines with dextromethorphan sold in the U.S., estimate 177 million packages of OTC medicines containing dextromethorphan were shipped in the U.S. in 2007, further illustrating the widespread use of this medicine.

³¹ The New DAWN Report, *supra*.

³² Id.

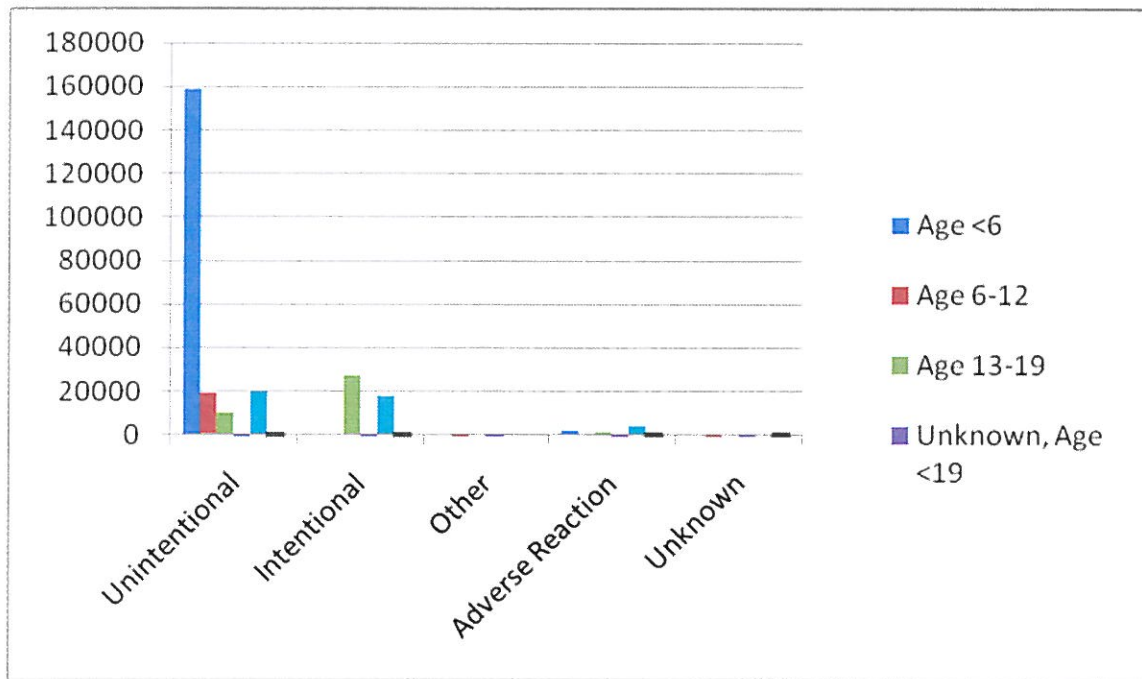
³³ See “Drug Abuse Warning Network, 2005: National Estimates of Drug-Related Emergency Department Visits,” Office of Applied Studies, SAMSHA, February 2007, finding rates per 100,000 population were 193 for the 12-17 age group; 335 for 18-20; 336 for 21-24; 312 for 25-29; and 283 for 30-34. Overall emergency department visits attributed by DAWN to nonmedical use of all pharmaceuticals continued at a rate of 289 per 100,000 population in the 35-44 age group – higher than the total for 12-20. ED visits involving dextromethorphan in this 35-44 age group

It is also notable that alcohol was implicated in 36 percent of emergency department visits involving nonmedical use of dextromethorphan for those aged 18-20 and in 13 percent of visits for those aged 12-17.³⁴

The number of calls placed to poison centers in the U.S. through the National Poison Data System (NPDS) of the American Association of Poison Control Centers is a second source of information on the public health impact of reported intentional abuse of dextromethorphan.

All calls placed to U.S. poison centers, regardless of outcome, are coded for the reported reason for the exposure. In a review of 260,514 dextromethorphan exposures from January 1, 2003 through December 31, 2007, the overwhelming majority of dextromethorphan cases (79.5 percent) were due to unintentional exposures (see figure 1).³⁵ The most common scenario in an unintentional exposure is a young child (under age 6) exploring their environment resulting in an unsupervised, accidental ingestion.³⁶

Figure 1. Reason for Dextromethorphan Exposures Reported to the National Poison Data System from 2003 through 2007



Intentional exposures were reported in 17.6 percent of cases, most often in the age 13-19 group.³⁷ These intentional exposures were further categorized by abuse, suspected suicide,

fall to one-third the level of those 21-34, and one-ninth the level of those 12-20. The New DAWN Report, *supra*, note 21.

³⁴ The New DAWN Report, *supra*.

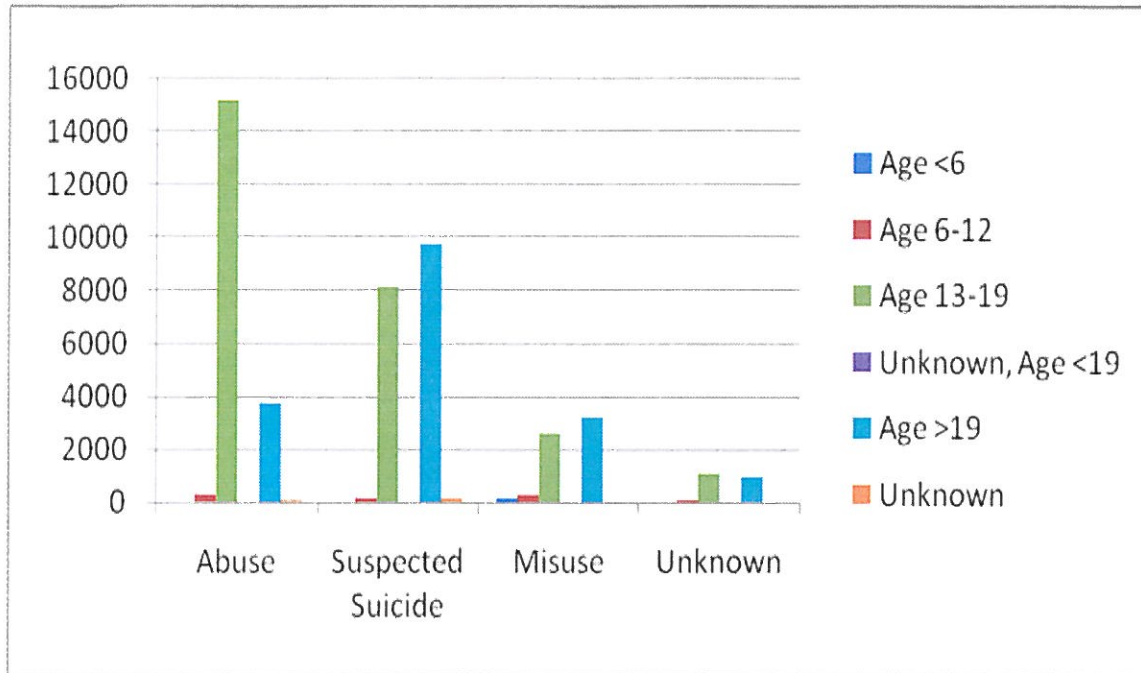
³⁵ Green, et al., "Intentional Abuse of Dextromethorphan as Reported to the National Poison Data System (NPDS)," Rocky Mountain Poison and Drug Center, October 2008, on file at CHPA.

³⁶ *Id.*

³⁷ *Id.*

misuse, and intentional unknown.³⁸ Of the approximately 46,000 intentional exposures over the five-year period, 42 percent were reports of intentional abuse.³⁹ Teens constituted 79 percent of the intentional abuse cases (see figure 2).⁴⁰

Figure 2. Intentional Dextromethorphan Exposures Reported to the National Poison Data System from 2003 through 2007



As to the health impact of intentional exposures (from all four categories, including intentional abuse) as reported by the medical outcome, intentional dextromethorphan exposures were most often reported as minor (31 percent) or moderate effects (26 percent).⁴¹ Major or life-threatening effects were reported in fewer than 2 percent of cases.⁴² A total of 24 deaths were reported following an intentional exposure, 0.01 percent of all dextromethorphan exposures, and 0.05 percent of intentional exposure cases.⁴³ A majority of patients in death cases associated with dextromethorphan were exposed to multiple substances beyond dextromethorphan.

Finally, the total number of dextromethorphan exposures reported to the NPDS decreased in 2006 and 2007 from a peak in 2005.⁴⁴

By comparison, NPDS exposures can number in to the thousands for all types of substances. Glow sticks, for example, were a nonpharmaceutical source of exposure for over

³⁸ Id.

³⁹ Id. (NPDS defines intentional abuse as an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect. Recreational use of a substance for any effect.)

⁴⁰ Id.

⁴¹ Id.

⁴² Id.

⁴³ Id.

⁴⁴ Id.

5,300 people age 6-19 – an age group beyond the age of curious young children accidentally seeking to ingest substances – in the 2006 NPDS annual report (as compared to approximately 7,500 for a given year in the case of dextromethorphan).⁴⁵

In short, while dextromethorphan intentional abuse exposures exist in the NPDS, they are not out of line with exposures seen with other substances, particularly given the size of the U.S. population and widespread, appropriate therapeutic use of dextromethorphan.

Dextromethorphan is not thought to be dependence-producing, and while Boyer’s review article states “susceptible individuals may develop craving and habitual use of the drug,” it similarly points out “dextromethorphan is not thought to have addictive properties.”⁴⁶ A separate review concluded dextromethorphan’s lack of dependence producing properties and its inability to produce abstinence syndromes was also demonstrated.⁴⁷ Fisher also notes that in three case reports raising a concern of possible psychological dependence, all three case report patients involved had a chronic history of “polydrug abuse.”⁴⁸ A set of animal studies in rats and monkeys suggest some phencyclidine-like behavioral effects, but the authors point out they are more reliably produced by a metabolite that is not commercially available.⁴⁹ In contrast to the Nicholson suggestion, an earlier review of preclinical abuse liability studies found rats and monkeys do not self-administer the drug, and morphine-dependent animals will not take dextromethorphan as a substitute.⁵⁰ Cicero stated “All of those [preclinical animal] tests have proven unequivocally that it does not produce primary dependence. It is not self-administered by animals, down from rats up through monkeys.”⁵¹

“Real world” experience also provides important support for the conclusion that dextromethorphan does not present dependence-producing potential. Data from the Utah Division of Substance Abuse and Mental Health on the primary substances used by clients entering treatment for alcohol or drug abuse or dependence found over-the-counter drugs constituted 0.1 percent – 29 out of over 19,000 people – of the primary substances of abuse.⁵² (This report included all OTC medicines as a category, and does not provide a breakdown of the

⁴⁵ See Bronstein, et al., “2006 Annual Report of the American Association of Poison Control Centers’ National Poison Data System (NPDS),” *Clinical Toxicology*, 45:8, December 2007, for the glow stick reference, and see Green, *supra*, from which approximately 7,500 cases a year is extrapolated.

⁴⁶ See Boyer, *supra*. In contrast, the original FDA OTC Review advisory panel which looked at dextromethorphan and other ingredients and cough and cold medicines noted abuse had been reported with very high doses, but no physical dependence had been reported. 41 Fed. Reg. 38340 (September 9, 1976).

⁴⁷ Fisher, “Dextromethorphan,” *Clinical Toxicology Review (Massachusetts Poison Control System)*, 13 (January 1991).

⁴⁸ *Id.*

⁴⁹ See Nicholson, et al., “Evaluation of the reinforcing properties and phencyclidine-like discriminative stimulus effects of dextromethorphan and dextrophan in rats and resus monkeys,” *Psychopharmacology*, 146: 49 (1999).

⁵⁰ See FDA Drug Abuse Advisory Committee member Cicero review, FDA Drug Abuse Advisory Committee meeting proceedings, July 14, 1992, at 208.

⁵¹ *Id.*

⁵² 2007 annual report of the Utah Division of Substance Abuse and Mental Health, 48 (available at www.dsamh.utah.gov). Further support for the lack of an indication of addiction issues is seen in a study of Tulare County, California, Drug Court clients, which found that none of the clients admitted to OTC medicines as their drug-of-choice. Lessenger, *supra*.

ingredients in the OTC drugs reported as the substance of purported abuse.) In contrast, oxycodone or hydrocodone constituted 2.8 percent of the primary substance abused.⁵³

While we do not believe international scheduling is needed, and despite the absence of indicators of a dependence-producing potential for this ingredient, we recognize our obligation as an industry to educate and raise awareness among consumers, parents, community leaders, and policymakers about medicine abuse, including abuse with dextromethorphan-containing cough medicine. It is for this reason that CHPA has established partnerships with such key organizations as the Partnership for a Drug-Free America, the Community Anti-Drug Coalitions of America, and D.A.R.E. America. These partnerships began in 2003 and include our comprehensive web site, www.StopMedicineAbuse.org, and an online grassroots campaign to help parents fight teen medicine abuse (www.FiveMoms.com). The single most important point of all of these awareness building activities is that the Partnership for a Drug-Free America has shown that children of parents who talk to them about drug abuse are half as likely to abuse substances to begin with.⁵⁴ The Partnership for a Drug-Free America is not alone in this conclusion that raising parents' awareness and encouraging parents to interact with their children is key. For instance, the 2007 National Survey of Drug Use and Health found past month use of illicit drugs, cigarettes, and alcohol was lower among youths aged 12 to 17 who reported that their parents always or sometimes engaged in monitoring behaviors than among youths whose parents "seldom" or "never" engaged in such behaviors.⁵⁵

3. Control of the substance

Dextromethorphan is not scheduled under the U.S. Controlled Substances Act (CSA). On the contrary, dextromethorphan was explicitly excluded from the CSA at the time of its passage. As the U.S. House of Representatives report on the bill noted:

“Subsection 811(g)(2) provides that the drug dextromethorphan is not to be deemed included in any of the schedules contained in Section 202 unless subsequently controlled after the date of enactment of Part B pursuant to the provisions of Section 201. This section is merely designed to insure that dextromethorphan, which is used in a number of cough syrups sold over the counter without a prescription, will not be controlled by virtue of its relationship to drugs already listed in the schedules on the date of enactment.”⁵⁶

The UN Single Convention on Narcotic Drugs, 1961, itself similarly includes a specific exclusion for dextromethorphan from scheduling.⁵⁷

⁵³ 2007 annual report of Utah DSAMH, *supra*.

⁵⁴ See Partnership for a Drug-Free America, http://www.drugfree.org/Portal/DrugIssue/Research/parent_teen_discussions/Launches_Time_To_Talk

⁵⁵ 2007 National Survey on Drug Use and Health: National Findings, Substance Abuse and Mental Health Services Administration, 2008.

⁵⁶ H.R. Rep. 91-1444 (September 10, 1970).

⁵⁷ Single Convention on Narcotic Drugs, 1961 (both the Single Convention as done at New York, March 30, 1961, and the Single Convention as amended by the 1972 Protocol include this exclusion).

The common thread of both the 1961 Single Convention and U.S. enactment of the Controlled Substances Act is that dextromethorphan was already an established substance in medicines whose use was known, and both those who adopted the 1961 Single Convention and the U.S. Congress not only chose not to schedule dextromethorphan, they made an affirmative decision to effectuate their judgment.

While dextromethorphan is not subject to controlled substance controls and while we are unaware of any reports of unfinished dextromethorphan being illegally diverted from the supply chain, we recognize there are reports of isolated incidences of teens purchasing the unfinished, bulk ingredient for intentional abuse. Because unfinished dextromethorphan can pose greater risk given unknown doses and an ability to take extremely excessive amounts, CHPA urged that legislation be introduced and supports bills before the U.S. Congress to make the illicit distribution of unfinished dextromethorphan illegal.⁵⁸ Neither the U.S. House of Representatives nor the U.S. Senate initiatives would schedule dextromethorphan in a finished product form. The House bill would prohibit possession or distribution of unfinished dextromethorphan by anyone who does not have a legitimate need for it without any controlled substance scheduling.

We are not aware of any reports of clandestine manufacture of dextromethorphan or smuggling.

4. Impact of scheduling

If dextromethorphan were placed under international controls, it would have a significant negative impact on its availability to treat coughs, as dextromethorphan is the most widely used cough suppressant in the U.S. While the OTC Review monograph includes codeine as an antitussive, the lowest dose of codeine is a Schedule V Controlled Substance in the U.S., and approximately half of the states in the U.S. require a prescription for Schedule V substances in their states. Higher doses of codeine are Schedule III. Driving Americans or citizens of other countries toward additional codeine use, which has been recognized as a substance of abuse and is listed in the 1961 Single Convention under schedule II, would have its own negative consequences.⁵⁹ For instance, a study comparing the effectiveness of dextromethorphan and codeine for cough in Europe reported that “in view of its lack of side-effects, its safety even in overdose and non-narcotic status, the increasing trend in Europe to use dextromethorphan as a substitute for codeine in the treatment of cough is to be welcomed.”⁶⁰

Under the relevant OTC Review monograph for antitussives, diphenhydramine, another ingredient which is generally recognized as safe and effective, is more commonly used as an antihistamine.⁶¹ Diphenhydramine also may cause marked drowsiness, which dextromethorphan

⁵⁸ See S. 2274, “Dextromethorphan Abuse Reduction Act of 2007”, H.R. 970, and CHPA hearing statement to the U.S. Senate Committee on the Judiciary Subcommittee on Crime and Drugs and the Senate Caucus on International Narcotics Control, March 2008.

⁵⁹ Single Convention on Narcotic Drugs, 1961, schedule II.

⁶⁰ Matthys, et al., “Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough,” J. Int. Med. Res. 11: 92 (1983).

⁶¹ See 21 CFR 341.14 for OTC antitussive ingredients.

does not, and diphenhydramine includes a greater number of drug interaction warnings.⁶² Chlopheniadol, the final ingredient generally recognized as safe and effective under the relevant OTC Review monograph, has not been used, to the best of our knowledge, as an OTC oral cough suppressant for decades in the U.S.⁶³ In other words, there is no practical substitute for dextromethorphan as a cough suppressant.

As an illustration of the impact of requiring controls of the type required for Schedule V substances in those states – roughly half – which do **not** require a prescription (i.e., pharmacist-only sale, logbooks, and record-keeping), the control of pseudoephedrine provides a partial parallel. While pseudoephedrine has not been the subject of abuse, because it can be diverted to manufacture methamphetamine, under the Combat Methamphetamine Epidemic Act of 2005, pseudoephedrine sales are subject to behind-the-counter placement, logbook, and record-keeping requirements, among others. In the first year after these controls were enacted, pseudoephedrine purchases for nasal decongestion dropped by 18 percent.⁶⁴ And if scheduling resulted in prescription status through U.S. Controlled Substances Act Schedule IV or Schedule III listing, a reduction in use and resulting doctor visits would be even higher.

Cough is already the most frequent complaint for which patients seek medical attention period.⁶⁵ If only one in 10 people today using a cough medicine without a prescription instead turned to a doctor, that could result in eight million additional physician visits in a three-month period.⁶⁶

Given dextromethorphan's place as the only practical oral cough suppressant in the U.S., impeding access to dextromethorphan would have a negative impact on the overall treatment of cough and cold symptoms. In 2007, approximately 211 million American households purchased over-the-counter medicines to self-treat cough, cold, flu, allergy, and sinus symptoms⁶⁷. Patients who self treat their cough and cold symptoms save the U.S. \$4.75 billion a year through improved work productivity, reducing unnecessary doctor visits, and taking prescription medicines only when appropriate.⁶⁸ Scheduling active ingredients in cough and cold medicines will upset this trend as the policy poses access challenges for legitimate consumers and could increase healthcare expenditures for the entire system. Requiring consumers to see a doctor for common cough and cold ailments and secure a prescription will drive up costs for patients, private insurance, managed care and state Medicaid programs. Private and public insurance may not cover visits for cough and cold symptoms forcing patients to pay a greater share of care.

⁶² See 21 CFR 341.74(c)(4)(ix)(B) for diphenhydramine sedation warning.

⁶³ See 21 CFR 341.14 for OTC antitussive ingredients. No references to the ingredient were found in a review of the *PDR for Nonprescription Drugs* dating back to the 1980 edition and a review of *The Handbook of Nonprescription Drugs*, American Pharmacists Association, dating back to the 1973 edition.

⁶⁴ See presentation by Stephen Johnson, Information Resources Inc., to CHPA Regulatory and Scientific Conference, May 10, 2007 (on file at CHPA).

⁶⁵ See D. Woodell, et al., "National ambulatory medical care survey: 2002 summary," in "Advanced Data from vital and Health Statistics," No. 346, Department of Health and Human Services, August 26, 2004.

⁶⁶ See Michaels Opinion Research, *supra*, for the basis of the doctor visit increase extrapolation.

⁶⁷ IRI, All Outlet Household Panel, 52 week Data Ending April 1, 2007.

⁶⁸ M. Lipksy, et al., "An Economic Analysis for Treating Viral Upper Respiratory Tract Infection in the United States," presentation to the World Self-Medication Industry Asia/Pacific regional conference, October 28, 2004 (and Northwestern University press release, October 26, 2004).

Also, private and public prescription programs may not cover over the counter medicines thus increasing out of pocket costs for patients, and the cost for medications could rise due to dispensing fees and other price increases due to labeling changes.

Furthermore, placing products behind a pharmacy counter cuts consumer access by as much as 85 percent since pharmacies only represent 15 percent of all retail stores; residents in rural areas may experience greater access challenges.

There are, of course, practical and costly implications of scheduling for manufacturers of medicines as well. These include increases in security requirements including cage or vault storage; producing special labels; and meeting the challenges a quota system places on a cough/cold category that is today organized to respond to high seasonal variability. All schedules require cage or vault storage for raw, unfinished ingredients as well as finished medicines. Since cough/cold medications are seasonal, any type of quota system will make it difficult for manufacturers to forecast usage. Current inventory and manufacturing systems are organized to respond to seasonal unpredictability in the marketplace. Since quotas require manufacturers to apply for additional raw ingredients when supplies are low – approval and shipping of these raw ingredients could delay, disrupt or totally suspend operations. This could result in inability to manufacture products and ship to stores, leaving store shelves empty and consumers unable to purchase medicines.

5. Remarks

Dextromethorphan does not present the types of issues envisioned in the UN Psychotropic Substance Convention assessment criteria:

- US experience does not indicate a sufficient level of dependence potential;
- there is little evidence of criminal activity associated with dextromethorphan;
- there is insufficient evidence that the substance is or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

On this final factor, we would note that the Commentaries to the Psychotropic Substance Convention state “it is apparent that only a *significant* health problem appears to be a 'public health' problem as this phrase is used by the Vienna Convention. . . .”⁶⁹ This is not the case with dextromethorphan.

The UN Convention on Psychotropic Substances is designed to address problems of an international character by providing countries with tools to attack trafficking, diversion, and related criminal activity. For dextromethorphan, these types of controls are not at issue. We

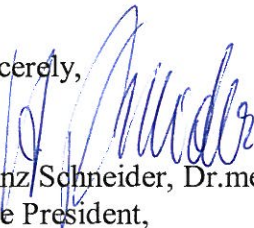
⁶⁹ Commentary on Convention on Psychotropic Substances, 1971, United Nations Publication E.76.XI.5, at 46.

have seen no signals of diversion or international trafficking. To the extent there are any indicators of local intentional abuse, there are no indicators that international controls would address the situation. Instead, in those isolated countries where intentional abuse has been reported, the course currently being taken in the U.S. provides a better solution: raising parental awareness. A second potential solution, as is being considered by the U.S. Congress, is to limit the availability where indicated on a nation-by-nation basis of the active pharmaceutical ingredient in its unfinished form only to those with a legitimate use for it.

If dextromethorphan nevertheless **were** to be subject to international scheduling, it would impede access and come at a great cost to citizens who use this safe, effective medicine to treat their coughs.

We urge the U.S. Government to recommend to the World Health Organization and its Expert Committee on Drug Dependence that dextromethorphan not move forward for further action after the April 2009 pre-review.

Sincerely,

A handwritten signature in blue ink, appearing to read "H. Schneider", is written over the typed name.

Heinz Schneider, Dr.med.
Vice President,
Regulatory & Scientific Affairs