The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We are bringing this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

M E M O R A N D U M
Department of Health and Human Services
FDA Center for Drug Evaluation and Research
Office of the Center Director

DATE: August 23, 2010

FROM: Michael Klein, Ph.D., Director
Controlled Substance Staff (CSS)

TO: Chair, Members and Invited Guests
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Overview of the September 14, 2010, DSaRM Advisory Committee Meeting to Discuss the Drug Enforcement Administration (DEA) Request for an Abuse Potential Evaluation and Scheduling Recommendation for Dextromethorphan (DXM)

At this meeting of the DSaRM Advisory Committee, we will discuss the abuse potential of DXM drug products. In accordance with the provisions of the Controlled Substances Act (CSA), the DEA has gathered and reviewed available data on DXM abuse and cited an increased incidence of abuse. DEA requested from the Assistant Secretary for Health, Department of Heath and Human Services (HHS), a scientific and medical evaluation and scheduling recommendation for DXM. The responsibility for conducting the scientific and medical evaluation of substances for control under the CSA is delegated to the FDA. FDA additionally requests input from the National Institute on Drug Abuse (NIDA) on drug scheduling recommendations.

The abuse of DXM products was discussed in two previous FDA advisory committees. In August 1990, an advisory committee was convened as a result of reports of abuse of DXM-containing cough syrups by teenagers in areas of Pennsylvania and Utah. The committee was asked to help FDA develop a strategy for assessing the problem and discuss possible solutions. The committee recommended that the sponsor provide additional data on the toxicity of the substance in the higher dose range, and that additional epidemiological data be gathered so that FDA could better assess the scope and significance of abuse, and the risk to the public health. In July 1992, the committee reconvened and discussed several proposed epidemiological studies on DXM abuse, including conducting a national survey from interviews with drug-free school coordinators, evaluating attitudes and behaviors of potential and actual DXM abusers and how they might be affected by an abuse prevention program. Although no clear consensus on the extent of the problem or solutions came out of this meeting, there was a general recognition, in this early pre-internet era, that outbreaks of abuse occurred in small communities, that the DXM abuse problem had not risen yet to the national level, and further studies should focus on areas where abuse outbreaks are occurring. FDA also encouraged clinical investigators to collect clinical behavioral pharmacology data as part of future clinical studies using high dose DXM.

Considering its widespread over the counter (OTC) availability, relatively few reports of serious abuse-related events involving DXM have been published. However, in 2005, five teenagers

from the states of Washington, Florida and Virginia were reported to have died following ingestion of DXM. In each case, the deaths were deemed to be the result of direct toxic effects of DXM powder. Other case reports of abuse and effects of overdose of DXM products are described in the literature. To warn the public about the risks associated with abuse of the drug, FDA published a Talk Paper ("FDA Warns Against Abuse of Dextromethorphan," May 20, 2005).

Starting in May 2006, the Consumer Healthcare Products Association (CHPA) began a number of voluntary initiatives to reduce the abuse of DXM by teens. The CHPA website describes steps aimed at preventing abuse, and is supported by data from the Partnership Attitude Tracking Study (PATS) survey. A number of reasonable efforts are made to get the abuse warning out. The Agency has reviewed information provided on the CHPA website and is providing comments.

After receiving DEA's request for a scheduling recommendation on DXM, FDA began to collect information to support an Agency assessment to respond to the request. We determined that the pharmacology of the drug in a range of doses needs to be reviewed, along with the clinical data related to its medical use. We requested that the CDER Office of Surveillance and Epidemiology (OSE) provide drug usage data and examine data bases and publications that document reports of abuse, misuse and overdose. DXM is available for use in a number of prescription products, as well as in its most common form as OTC products for the treatment of cough. However, according to a provision of the CSA, 21 USC 811(g), non-narcotic substances sold OTC without prescription shall by regulation be excluded from scheduling. Thus, it is unclear that the scheduling of the OTC cough products are permitted under the CSA.

We are requesting that you help us determine if the pharmacology and epidemiology data presented are sufficient to demonstrate that DXM has abuse potential and if the data identify a particular population at risk for its abuse. Also we welcome your evaluation of the effectiveness of voluntary efforts in reducing DXM abuse and recommendations of any new measures that could further reduce abuse and misuse of these products. Also, we would like you to consider the impact of additional risk management measures on drug availability and patient care. Finally, you will be asked for your recommendation on whether DXM should be placed into a schedule of the CSA.

The following documents are included in this package to address the above issues:

1. DEA summary of concerns
2. CSA and the list of substances in each schedule of the CSA
3. OTC monograph & NDA approval process: DXM history
4. Abuse-related pharmacology
5. Clinical perspective in the treatment of cough
6. Drug utilization data
7. Drug Abuse Warning Network (DAWN) data
8. Adverse events reporting system (AERS) data
9. Review of the CHPA website

We thank you in advance for participating in this meeting and providing us with your expertise and insights on this important public health issue.

FDA Talk Paper

T05-23
May 20, 2005

Media Inquiries: Bradford Stone
301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Warns Against Abuse of Dextromethorphan (DXM)

The Food and Drug Administration (FDA) is concerned about the abuse of dextromethorphan (DXM), a synthetically produced ingredient found in many over-the-counter (OTC) cough and cold remedies. The agency is working with other health and law enforcement authorities to address this serious issue and warn the public of potential harm, after five recently reported deaths of teenagers that may be associated with the consumption of powdered DXM sold in capsules.

Although DXM, when formulated properly and used in small amounts, can be safely used in cough suppressant medicines, abuse of the drug can cause death as well as other serious adverse events such as brain damage, seizure, loss of consciousness, and irregular heart beat.

DXM abuse, though not a new phenomenon, has developed into a disturbing new trend which involves the sale of pure DXM in powdered form. This pure DXM is often encapsulated by the [] dealer[] and offered for street use.

DXM has gradually replaced codeine as the most widely used cough suppressant in the United States . It is available OTC in capsule, liquid, liquid gelatin capsule, lozenge, and tablet forms. When ingested at recommended dosage levels, DXM is generally a safe and effective cough suppressant.

Additional information about the dangers of Dextromethorphan use and abuse can be found at the following SAMHSA National Clearinghouse for Alcohol and Drug Information links. http://store.health.org/catalog/mediaDetails.aspx?ID=371, http://www.family.samhsa.gov/get/otcdrugs.aspx.

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DRAFT QUESTIONS TO COMMITTEE:

1. Are the pharmacology data (including receptor binding, animal behavioral effects and human behavioral effects) and the epidemiology data sufficient to demonstrate that DXM has abuse potential? Do the data identify a particular population at risk for abuse of DXM? (DISCUSS)

2. How effective do you believe the CHPA (Consumer Healthcare Products Association) program (http://www.chpa-info.org/issues/DXM_Overview.aspx) is in reducing abuse of DXM? Do you have any recommendations for modifying this program or implementing any new measures to further reduce abuse and misuse of these products? What effect do you believe that any of these efforts would have on drug availability and patient care? (DISCUSS)

3. In consideration of issues discussed above, do you recommend that DXM be scheduled in the CSA? (VOTE)

Dextromethorphan

Dextromethorphan (3-methoxy-N-methylmorphinan) is one of the most widely used antitussive (cough suppressant) agents, worldwide. It was approved for use by the Food and Drug Administration in 1958 as a non-prescription cough medication. Dextromethorphan is not scheduled under the Controlled Substances Act. Currently, dextromethorphan is found in more than 125 over-the-counter (OTC) cough/cold patented products. Medications are available in pills, gel caps, lozenges, liquids and syrups, either alone or in combination with analgesics (acetaminophen), antihistamines (brompheniramine, chlorpheniramine, and diphenhydramine), decongestants (pseudoephedrine) and/or expectorants (guaifenesin). Dextromethorphan is also available in bulk powder from Internet sites.

DEA is concerned with the increasing abuse of dextromethorphan, especially among adolescents. Dextromethorphan abuse is often referred to as "robo-tripping", "tussing", or "skittling" named after the dextromethorphan-containing products, Robotussin and Coricidin. These and other dextromethorphan-containing cough preparations are abused for their euphoriant and hallucinogenic properties, which is generally associated with doses 10-20 times greater than the dose recommended for cough suppression (10-30 mg).

The **National Forensic Laboratory Information System (NFLIS)** and the **System to Retrieve Information From Drug Evidence (STRIDE)** are DEA databases that collect scientifically verified data on analyzed samples in state and local (NFLIS), and federal (STRIDE) forensic laboratories. From 2003 to 2009, the federal, state and local forensic laboratories reported a 201 % increase of dextromethorphan exhibits, from 88 in 2003 to 265 in 2009.

DEXTROMETHORPHAN SEIZED
(Number of Items/Exhibits)

Source	*2003*	*2004*	*2005*	*2006*	*2007*	*2008*	*2009*
NFLIS – State/Local	64	90	154	97	104	142	236
STRIDE – Federal	24	71	69	50	24	44	29
TOTAL	**88**	**161**	**223**	**147**	**128**	**186**	**265**

Data Source: NFLIS & STRIDE, queried 06/25/2010

IMS National Prescription Audit Plus™, a provider database managed by IMS America, estimates total U.S. dispensed prescriptions. Dextromethorphan is primarily purchased as an OTC medication requiring no medical prescription. This prescription data does not capture the OTC market, so the data underestimate dextromethorphan use in the U.S. In 2008, there were approximately 13.2 million dextromethorphan medications dispensed in the U.S. In 2009, IMS estimates that 14.9 million dextromethorphan medications were dispensed.

ESTIMATED TOTAL DISPENSED DEXTROMETHORPHAN
(Numbers in Thousands)

2004	*2005*	*2006*	*2007*	*2008*	*2009*
15,757	17,619	15,568	14,876	13,205	14,923

DEA establishes **Aggregate Production Quota** for the maximum amount of Schedule I and II substances which may be manufactured in the United States for legitimate national scientific, medical and export needs, and for the maintenance of stocks. Since it is a non-controlled drug, DEA does not establish quota for dextromethorphan.

National Survey on Drug Use and Health (NSDUH, formerly the National Household Survey on Drug Abuse) is a Substance Abuse and Mental Health Services Administration (SAMHSA) system that measures drug use by people living in households. No data are available regarding the abuse of dextromethorphan.

A National Institute on Drug Abuse-funded study conducted by the University of Michigan, **Monitoring the Future (MTF),** measures prevalence of drug use among eighth, tenth, and twelfth grade students. Although the MTF survey does not report specifically on dextromethorphan, it includes data on over-the-counter (OTC) cough and cold medicine. The 2009 MTF reported that the annual prevalence of non-medical use of cough and cold among students in 8th, 10th, and 12th grades was 2.6%, 5.0%, and 6.3%, respectively. These percentages are not statistically significantly different from those reported in 2008.

The **American Association of Poison Control Centers** (AAPCC) data suggest that dextromethorphan products are involved in a number of toxic exposures. In 2007, there were 59,474 case mentions and 46,536 single exposures associated with dextromethorphan, as reported by the AAPCC. The following year, AAPCC reported a decrease in case mentions and single exposures. There were 52,991 case mentions and 40,229 single exposures related to dextromethorphan in 2008, according to AAPCC.

Dextromethorphan
Drug Fact Sheet

The **Drug Abuse Warning Network (DAWN)** is a Substance Abuse and Mental Health Services Administration (SAMHSA) surveillance system that monitors drug-related visits to hospital emergency departments (EDs) for the Nation and selected metropolitan areas. In 2003, DAWN was redesigned to expand beyond drug abuse. Major changes included changes in the case definition, case types, data collection methodology and sample. Thus, data collected and reported after 2003 should not be compared to data collected before that time. DAWN data from 2003 is not reported. The most recent year for which DAWN ED drug estimates are available, is 2008.

NATIONAL ESTIMATES OF DEXTROMETHORPHAN ED VISITS
(Old DAWN ED)

1998	1999	2000	2001	2002
1,926	1,008	1,703	1,769	2,324

Data Source: SAMHSA, Drug Abuse Warning Network, Hospital Emergency Room Reports

According to the New DAWN ED Dextromethorphan Special Topics Report *(November 2006, revised June 2009)*, it is estimated that non-medical use of dextromethorphan accounted for 35% of the estimated 16,858 total dextromethorphan visits in 2004. Other 2004 estimated dextromethorphan ED visits resulted from adverse reactions (31%), accidental ingestion (15%) and suicide attempt (17%). Further, 51% of the dextromethorphan non-medical visits involved patients aged 12-20.

NATIONAL ESTIMATES OF NON-MEDICAL DEXTROMETHORPHAN ED VISITS
(New DAWN ED)

2004	2005	2006	2007	2008
4,634	7,603	7,739	10,410	7,988

Data Source: SAMHSA, Drug Abuse Warning Network, Emergency Department, Detailed Tables, https://dawninfo.samhsa.gov/data, website accessed 07-13-2010.

*The estimated DAWN ED visits are derived from non-medical use of dextromethorphan, taken as a cough suppressant, alone, or in combination with upper respiratory medications.

For additional information, contact the Drug Enforcement Administration, Office of Diversion Control, Drug and Chemical Evaluation Section (ODE) at 202-307-7183 or ODE@usdoj.gov.

Drug Enforcement Administration
Office of Diversion Control
Drug & Chemical Evaluation Section
Springfield, Virginia 22152

DEXTROMETHORPHAN

(Street Names: DXM, CCC, Triple C, Skittles, Robo, Poor Man's PCP)

August 2010
DEA/OD/ODE

Introduction:

Dextromethorphan (DXM) is an over-the-counter (OTC) cough suppressant found in cold medications. DXM is often abused in high doses by adolescents to generate euphoria and visual and auditory hallucinations. Illicit use of DXM is referred to on the street as "Robo-tripping" or "skittling." These terms are derived from the most commonly abused products, Robitussin and Coricidin.

Licit Uses:

DXM is an antitussive found in more than 120 OTC cold medications either alone or in combination with other drugs such as analgesics (e.g. acetaminophen), antihistamines (e.g. chlorpheniramine), decongestants (e.g. pseudoephedrine) and/or expectorants (e.g. guaifenesin). The typical antitussive adult dose is 15 or 30 mg taken three to four times daily. The antitussive effects of DXM persist for 5 to 6 hours after oral administration. When taken as directed, side-effects are rarely observed. IMS Health™ reports a decrease in total dispensed prescriptions of DXM from 17.6 million in 2005 to 14.9 million in 2009.

Illicit Use:

The abuse of DXM is fueled by its OTC availability and extensive "how-to" abuse information on various web sites. The sale of the powdered form of DXM over the Internet poses additional risks due to the uncertainty of composition and dose.

DXM abusers report a heightened sense of perceptual awareness, altered time perception, and visual hallucinations. The typical clinical presentation of DXM intoxication involves hyperexcitability, lethargy, ataxia, slurred speech, sweating, hypertension, and/or nystagmus. Abuse of combination DXM products also results in health complications from the other active ingredient(s), which include increased blood pressure from pseudoephedrine, potential delayed liver damage from acetaminophen, and central nervous system toxicity, cardiovascular toxicity and anticholinergic toxicity from antihistamines. The abuse of high doses of DXM in combination with alcohol or other drugs is particularly dangerous and deaths have been reported.

Abusers of DXM describe four dose-dependent "plateaux:"

Plateau	Dose (mg)	Behavioral Effects
1st	100–200	Mild stimulation
2nd	200–400	Euphoria and hallucinations
3rd	300– 600	Distorted visual perceptions Loss of motor coordination
4th	500-1500	Dissociative sedation

According to the American Association of Poison Control Centers, there were 52,991 case mentions and 40,229 single exposures related to DXM in 2008.The Drug Abuse Warning Network (DAWN ED) reports that an estimated 7,739 emergency department visits were associated with non-medical use of dextromethorphan in 2006, 10,410 visits in 2007 and 7,988 visits in 2008.

Chemistry/Pharmacology:

DXM (d-3-methoxy-N-methyl-morphinan) is the dextro isomer of levomethorphan, a semisynthetic morphine derivative. Although structurally similar to other narcotics, DXM does not act as an opioid receptor agonist (e.g. morphine, heroin). DXM and its metabolite, dextrorphan, act as potent blockers of the N-methyl-d-aspartate (NMDA) receptor. At high doses, the pharmacology of DXM is similar to those of the controlled substances phencyclidine (PCP) and ketamine that also antagonize the NMDA receptor. High doses of DXM produce PCP-like behavioral effects. DXM may cause a false positive test result with some urine immunoassays for PCP.

Approximately 5-10% of Caucasians are poor DXM metabolizers which increases their risk for overdoses and deaths. DXM should not be taken with antidepressants due to the risk of inducing a life threatening serotonergic syndrome.

User Population:

Abuse of DXM occurs in all age groups but is most prevalent in youth and adolescents. A 6-year retrospective study from 1999 to 2004 of the California Poison Control System (CPCS) showed a 10-fold increase in the rate of CPCS DXM abuse cases in all ages and a 15-fold increase in the rate of CPCS DXM abuse cases in adolescents. In 2004, CPCS reported 1,382 DXM abuse cases.

The 2009 Monitoring the Future (MTF) Report indicated that the annual prevalence of non-medical use of cough and cold among students in 8th, 10th, and 12th grades was 2.6%, 5.0%, and 6.3%, respectively.

DAWN ED reports that, in 2004, the rate of ED visits resulting from nonmedical use of DXM for those aged 12 to 20 was 8.0 visits per 100,000 population, compared with 2.5 visits or fewer per 100,000 for other age groups.

Illicit Distribution:

DXM abuse often occurs with the OTC liquid cough preparations. More recently, abuse of tablet and gel capsule preparations has increased. DXM powder sold over the Internet is also a source of DXM for abuse. DXM is also distributed in illicitly manufactured tablets, containing only DXM or mixed with other illicit drugs such as ecstasy or methamphetamine.

According to the National Forensic Laboratory Information System (NFLIS) and the System to Retrieve Information from Drug Evidence (STRIDE), federal, state and local forensic laboratories analyzed 190 dextromethorphan exhibits that were submitted in 2008 and 279 exhibits that were submitted in 2009.

Control Status:

DXM is not scheduled under the Controlled Substances Act (CSA). However, the CSA indicated that DXM could be added to the CSA, in the future, through the traditional scheduling process, if warranted.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 202-353-1263, telephone 202-307-7183 or Email ODE@usdoj.gov.

Title 21 United States Code (USC)
Controlled Substances Act

Part B -- Authority to Control; Standards and Schedules

From the U.S. Code Online via GPO Access
[www.gpoaccess.gov]
[Laws in effect as of January 3, 2007]
[CITE: 21USC811]

Section 811. Authority and Criteria for Classification of Substances

(a) Rules and regulations of Attorney General; hearing

The Attorney General shall apply the provisions of this subchapter to the controlled substances listed in the schedules established by section 812 of this title and to any other drug or other substance added to such schedules under this subchapter. Except as provided in subsections (d) and (e) of this section, the Attorney General may by rule--

(1) add to such a schedule or transfer between such schedules any drug or other substance if he--

(A) finds that such drug or other substance has a potential for abuse, and

(B) makes with respect to such drug or other substance the findings prescribed by

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subsection (b) of section 812 of this title for the schedule in which such drug is to be placed; or

(2) remove any drug or other substance from the schedules if he finds that the drug or other substance does not meet the requirements for inclusion in any schedule.

Rules of the Attorney General under this subsection shall be made on the record after opportunity for a hearing pursuant to the rulemaking procedures prescribed by subchapter II of chapter 5 of title 5. Proceedings for the issuance, amendment, or repeal of such rules may be initiated by the Attorney General (1) on his own motion, (2) at the request of the Secretary, or (3) on the petition of any interested party.

(b) Evaluation of drugs and other substances

The Attorney General shall, before initiating proceedings under subsection (a) of this section to control a drug or other substance or to remove a drug or other substance entirely from the schedules, and after gathering the necessary data, request from the Secretary a scientific and medical evaluation, and his

recommendations, as to whether such drug or other substance should be so controlled or removed as a controlled substance. In making such evaluation and recommendations, the Secretary shall consider the factors listed in paragraphs (2), (3), (6), (7), and (8) of subsection (c) of this section and any scientific or medical considerations involved in paragraphs (1), (4), and (5) of such subsection. The recommendations of the Secretary shall include recommendations with respect to the appropriate schedule, if any, under which such drug or other substance should be listed. The evaluation and the recommendations of the Secretary shall be made in writing and submitted to the Attorney General within a reasonable time. The recommendations of the Secretary to the Attorney General shall be binding on the Attorney General as to such scientific and medical matters, and if the Secretary recommends that a drug or other substance not be controlled, the Attorney General shall not control the drug or other substance. If the Attorney General determines that these facts and all other relevant data constitute substantial evidence of potential for abuse such as to warrant control or substantial evidence that the drug or other substance should be removed entirely from the schedules, he shall initiate proceedings for control or removal, as the case may be, under subsection (a) of this section.

(c) Factors determinative of control or removal from schedules

In making any finding under subsection (a) of this section or under subsection (b) of section 812 of this title, the Attorney General shall consider the following factors with respect to each drug or other substance proposed to be controlled or removed from the schedules:

(1) Its actual or relative potential for abuse.

(2) Scientific evidence of its pharmacological effect, if known.

(3) The state of current scientific knowledge regarding the drug or other substance.

(4) Its history and current pattern of abuse.

(5) The scope, duration, and significance of abuse.

(6) What, if any, risk there is to the public health.

(7) Its psychic or physiological dependence liability.

(8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter.

(d) International treaties, conventions, and protocols requiring control; procedures respecting changes in drug schedules of Convention on Psychotropic Substances

(1) If control is required by United States obligations under international treaties, conventions, or protocols in effect on October 27, 1970, the Attorney

General shall issue an order controlling such drug under the schedule he deems most appropriate to carry out such obligations, without regard to the findings required by subsection (a) of this section or section 812(b) of this title and without regard to the procedures prescribed by subsections (a) and (b) of this section.

(2)(A) Whenever the Secretary of State receives notification from the Secretary-General of the United Nations that information has been transmitted by or to the World Health Organization, pursuant to article 2 of the Convention on Psychotropic Substances, which may justify adding a drug or other substance to one of the schedules of the Convention, transferring a drug or substance from one schedule to another, or deleting it from the schedules, the Secretary of State shall immediately transmit the notice to the Secretary of Health and Human Services who shall publish it in the Federal Register and provide opportunity to interested persons to submit to him comments respecting the scientific and medical evaluations which he is to prepare respecting such drug or substance. The Secretary of Health and Human Services shall prepare for transmission through the Secretary of State to the World Health Organization such medical and scientific evaluations as may be appropriate regarding the possible action that could be proposed by the World Health Organization respecting the drug or substance with respect to which a notice was transmitted under this subparagraph.

(B) Whenever the Secretary of State receives information that the Commission on Narcotic Drugs of the United Nations proposes to decide whether to add a drug or other substance to one of the schedules of the Convention, transfer a drug or substance from one schedule to another, or delete it from the schedules, the Secretary of State shall transmit timely notice to the Secretary of Health and Human Services of such information who shall publish a summary of such information in the Federal Register and provide opportunity to interested persons to submit to him comments respecting the recommendation which he is to furnish, pursuant to this subparagraph, respecting such proposal. The Secretary of Health and Human Services shall evaluate the proposal and furnish a recommendation to the Secretary of State which shall be binding on the representative of the United States in discussions and negotiations relating to the proposal.

(3) When the United States receives notification of a scheduling decision pursuant to article 2 of the Convention on Psychotropic Substances that a drug or other substance has been added or transferred to a schedule specified in the notification or receives notification (referred to in this subsection as a "schedule notice") that existing legal controls applicable under this subchapter to a drug or substance and the controls required by the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 301 et seq.] do not meet the requirements of the schedule of the Convention in which such drug or substance has been placed, the Secretary of Health and Human Services after consultation with the Attorney General, shall first determine whether existing legal controls under this subchapter applicable to the drug or substance and the controls required

by the Federal Food, Drug, and Cosmetic Act, meet the requirements of the schedule specified in the notification or schedule notice and shall take the following action:

(A) If such requirements are met by such existing controls but the Secretary of Health and Human Services nonetheless believes that more stringent controls should be applied to the drug or substance, the Secretary shall recommend to the Attorney General that he initiate proceedings for scheduling the drug or substance, pursuant to subsections (a) and (b) of this section, to apply to such controls.

(B) If such requirements are not met by such existing controls and the Secretary of Health and Human Services concurs in the scheduling decision or schedule notice transmitted by the notification, the Secretary shall recommend to the Attorney General that he initiate proceedings for scheduling the drug or substance under the appropriate schedule pursuant to subsections (a) and (b) of this section.

(C) If such requirements are not met by such existing controls and the Secretary of Health and Human Services does not concur in the scheduling decision or schedule notice transmitted by the notification, the Secretary shall--

(i) if he deems that additional controls are necessary to protect the public health and safety, recommend to the Attorney General that he initiate proceedings for scheduling the drug or substance pursuant to subsections (a) and (b) of this section, to apply such additional controls;

(ii) request the Secretary of State to transmit a notice of qualified acceptance, within the period specified in the Convention, pursuant to paragraph 7 of article 2 of the Convention, to the Secretary-General of the United Nations;

(iii) request the Secretary of State to transmit a notice of qualified acceptance as prescribed in clause (ii) and request the Secretary of State to ask for a review by the Economic and Social Council of the United Nations, in accordance with paragraph 8 of article 2 of the Convention, of the scheduling decision; or

(iv) in the case of a schedule notice, request the Secretary of State to take appropriate action under the Convention to initiate proceedings to remove the drug or substance from the schedules under the Convention or to transfer the drug or substance to a schedule under the Convention different from the one specified in the schedule notice.

(4)(A) If the Attorney General determines, after consultation with the Secretary of Health and Human Services, that proceedings initiated under recommendations made under paragraph \1\ (B) or (C)(i) of paragraph (3) will not be completed within the time period required by paragraph 7 of article 2 of the Convention, the Attorney General, after consultation with the Secretary

and after providing interested persons opportunity to submit comments respecting the requirements of the temporary order to be issued under this sentence, shall issue a temporary order controlling the drug or substance under schedule IV or V, whichever is most appropriate to carry out the minimum United States obligations under paragraph 7 of article 2 of the Convention. As a part of such order, the Attorney General shall, after consultation with the Secretary, except such drug or substance from the application of any provision of part C of this subchapter which he finds is not required to carry out the United States obligations under paragraph 7 of article 2 of the Convention. In the case of proceedings initiated under subparagraph (B) of paragraph (3), the Attorney General, concurrently with the issuance of such order, shall request the Secretary of State to transmit a notice of qualified acceptance to the Secretary-General of the United Nations pursuant to paragraph 7 of article 2 of the Convention. A temporary order issued under this subparagraph controlling a drug or other substance subject to proceedings initiated under subsections (a) and (b) of this section shall expire upon the effective date of the application to the drug or substance of the controls resulting from such proceedings.

\1\ So in original. Probably should be "subparagraph".

(B) After a notice of qualified acceptance of a scheduling decision with respect to a drug or other substance is transmitted to the Secretary-General of the United Nations in accordance with clause (ii) or (iii) of paragraph (3)(C) or after a request has been made under clause (iv) of such paragraph with respect to a drug or substance described in a schedule notice, the Attorney General, after consultation with the Secretary of Health and Human Services and after providing interested persons opportunity to submit comments respecting the requirements of the order to be issued under this sentence, shall issue an order controlling the drug or substance under schedule IV or V, whichever is most appropriate to carry out the minimum United States obligations under paragraph 7 of article 2 of the Convention in the case of a drug or substance for which a notice of qualified acceptance was transmitted or whichever the Attorney General determines is appropriate in the case of a drug or substance described in a schedule notice. As a part of such order, the Attorney General shall, after consultation with the Secretary, except such drug or substance from the application of any provision of part C of this subchapter which he finds is not required to carry out the United States obligations under paragraph 7 of

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article 2 of the Convention. If, as a result of a review under paragraph 8 of article 2 of the Convention of the scheduling decision with respect to which a

notice of qualified acceptance was transmitted in accordance with clause (ii) or (iii) of paragraph (3)(C)--

(i) the decision is reversed, and

(ii) the drug or substance subject to such decision is not required to be controlled under schedule IV or V to carry out the minimum United States obligations under paragraph 7 of article 2 of the Convention, the order issued under this subparagraph with respect to such drug or substance shall expire upon receipt by the United States of the review decision. If, as a result of action taken pursuant to action initiated under a request transmitted under clause (iv) of paragraph (3)(C), the drug or substance with respect to which such action was taken is not required to be controlled under schedule IV or V, the order issued under this paragraph with respect to such drug or substance shall expire upon receipt by the United States of a notice of the action taken with respect to such drug or substance under the Convention.

(C) An order issued under subparagraph (A) or (B) may be issued without regard to the findings required by subsection (a) of this section or by section 812(b) of this title and without regard to the procedures prescribed by subsection (a) or (b) of this section.

(5) Nothing in the amendments made by the Psychotropic Substances Act of 1978 or the regulations or orders promulgated thereunder shall be construed to preclude requests by the Secretary of Health and Human Services or the Attorney General through the Secretary of State, pursuant to article 2 or other applicable provisions of the Convention, for review of scheduling decisions under such Convention, based on new or additional information.

(e) Immediate precursors

The Attorney General may, without regard to the findings required by subsection (a) of this section or section 812(b) of this title and without regard to the procedures prescribed by subsections (a) and (b) of this section, place an immediate precursor in the same schedule in which the controlled substance of which it is an immediate precursor is placed or in any other schedule with a higher numerical designation. If the Attorney General designates a substance as an immediate precursor and places it in a schedule, other substances shall not be placed in a schedule solely because they are its precursors.

Abuse Potential

(f) Abuse potential

If, at the time a new-drug application is submitted to the Secretary for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, it appears that such drug has an abuse potential, such information shall be forwarded by the Secretary to the Attorney General.

(g) Exclusion of non-narcotic substances sold over the counter without a prescription; dextromethorphan; exemption of substances lacking abuse potential

(1) The Attorney General shall by regulation exclude any non- narcotic drug which contains a controlled substance from the application of this subchapter and subchapter II of this chapter if such drug may, under the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 301 et seq.], be lawfully sold over the counter without a prescription.

(2) Dextromethorphan shall not be deemed to be included in any schedule by reason of enactment of this subchapter unless controlled after October 27, 1970 pursuant to the foregoing provisions of this section.

(3) The Attorney General may, by regulation, exempt any compound, mixture, or preparation containing a controlled substance from the application of all or any part of this subchapter if he finds such compound, mixture, or preparation meets the requirements of one of the following categories:

(A) A mixture, or preparation containing a nonnarcotic controlled substance, which mixture or preparation is approved for prescription use, and which contains one or more other active ingredients which are not listed in any schedule and which are included therein in such combinations, quantity, proportion, or concentration as to vitiate the potential for abuse.

(B) A compound, mixture, or preparation which contains any controlled substance, which is not for administration to a human being or animal, and which is packaged in such form or concentration, or with adulterants or denaturants, so that as packaged it does not present any significant potential for abuse.

(C) Upon the recommendation of the Secretary of Health and Human Services, a compound, mixture, or preparation which contains any anabolic steroid, which is intended for administration to a human being or an animal, and which, because of its concentration, preparation, formulation or delivery system, does not present any significant potential for abuse.

(h) Temporary scheduling to avoid imminent hazards to public safety

(1) If the Attorney General finds that the scheduling of a substance in schedule I on a temporary basis is necessary to avoid an imminent hazard to the public safety, he may, by order and without regard to the requirements of subsection (b) of this section relating to the Secretary of Health and Human Services, schedule such substance in schedule I if the substance is not listed in any other schedule in section 812 of this title or if no exemption or approval is in effect for the substance under section 505 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355]. Such an order may not be issued before the expiration of thirty days from--

(A) the date of the publication by the Attorney General of a notice in the Federal Register of the intention to issue such order and the grounds upon which such order is to be issued, and

(B) the date the Attorney General has transmitted the notice required by paragraph (4).

(2) The scheduling of a substance under this subsection shall expire at the end of one year from the date of the issuance of the order scheduling such substance, except that the Attorney General may, during the pendency of proceedings under subsection (a)(1) of this section with respect to the substance, extend the temporary scheduling for up to six months.

(3) When issuing an order under paragraph (1), the Attorney General shall be required to consider, with respect to the finding of an imminent hazard to the public safety, only those factors set forth in paragraphs (4), (5), and (6) of subsection (c) of this section, including actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution.

(4) The Attorney General shall transmit notice of an order proposed to be issued under paragraph (1) to the Secretary of Health and Human Services. In issuing an order under paragraph (1), the Attorney General shall take into consideration any comments submitted by the Secretary in response to a notice transmitted pursuant to this paragraph.

(5) An order issued under paragraph (1) with respect to a substance shall be vacated upon the conclusion of a subsequent rulemaking proceeding initiated under subsection (a) of this section with respect to such substance.

(6) An order issued under paragraph (1) is not subject to judicial review.

(Pub. L. 91-513, title II, Sec. 201, Oct. 27, 1970, 84 Stat. 1245; Pub. L. 95-633, title I, Sec. 102(a), Nov. 10, 1978, 92 Stat. 3769; Pub. L. 96-88, title V, Sec. 509(b), Oct. 17, 1979, 93 Stat. 695; Pub. L. 98- 473, title II, Secs. 508, 509(a), Oct. 12, 1984, 98 Stat. 2071, 2072; Pub. L. 108-358, Sec. 2(b), Oct. 22, 2004, 118 Stat. 1663.)

References in Text

This subchapter, referred to in subsecs. (a), (c)(8), (d)(3), (4)(A), (B), and (g)(2), (3), was in the original "this title", meaning title II of Pub. L. 91-513, Oct. 27, 1970, 84 Stat. 1242, as amended, and is popularly known as the "Controlled Substances Act". For complete classification of title II to the Code, see second paragraph of Short Title note set out under section 801 of this title and Tables.

The Federal Food, Drug, and Cosmetic Act, referred to in subsecs. (d)(3) and (g)(1), is act June 25, 1938, ch. 675, 52 Stat. 1040, as amended, which is classified generally to chapter 9 (Sec. 301 et seq.) of this title. For complete classification of this Act to the Code, see section 301 of this title and Tables.

Schedules I, IV, and V, referred to in subsecs. (d)(4)(A), (B), and (h)(1), are set out in section 812(c) of this title.

The Psychotropic Substances Act of 1978, referred to in subsec. (d)(5), is Pub. L. 95-633, Nov. 10, 1978, 92 Stat. 3768, which enacted sections 801a, 830, and 852 of this title, amended sections 352, 802, 811, 812, 823, 827, 841 to 843, 872, 881, 952, 953, and 965 of this title and section 242a of Title 42, The Public Health and Welfare, repealed section 830 of this title effective Jan. 1, 1981, and enacted provisions set out as notes under sections 801, 801a, 812, and 830 of this title. For complete classification of this Act to the Code, see Short Title of 1978 Amendment note set out under section 801 of this title and Tables.

This subchapter and subchapter II of this chapter, referred to in subsec. (g)(1), was in the original "titles II and III of the Comprehensive Drug Abuse Prevention and Control Act", which was translated as meaning titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, Pub. L. 91-513, Oct. 27, 1970, 84 Stat. 1242, 1285, as amended, to reflect the probable intent of Congress. Title II is classified principally to this subchapter and part A of title III comprises subchapter II of this chapter. For complete classification of this Act to the Code, see Short Title notes set out under section 801 of this title and Tables.

Amendments

2004--Subsec. (g)(1). Pub. L. 108-358, Sec. 2(b)(1), substituted "drug which contains a controlled substance from the application of this subchapter and subchapter II of this chapter if such drug" for "substance from a schedule if such substance".

Subsec. (g)(3)(C). Pub. L. 108-358, Sec. 2(b)(2), added subpar. (C).

1984--Subsec. (g)(3). Pub. L. 98-473, Sec. 509(a), added par. (3). Subsec. (h). Pub. L. 98-473, Sec. 508, added subsec. (h).

1978--Subsec. (d). Pub. L. 95-633 designated existing provisions as par. (1) and added pars. (2) to (5).

Change of Name

"Secretary of Health and Human Services" substituted for "Secretary of Health, Education, and Welfare" in subsec. (d)(2), (3), (4)(A), (B), (5) pursuant to section 509(b) of Pub. L. 96-88 which is classified to section 3508(b) of Title 20, Education.

Effective Date of 2004 Amendment

Amendment by Pub. L. 108-358 effective 90 days after Oct. 22, 2004, see section 2(d) of Pub. L. 108-358, set out as a note under section 802 of this title.

Effective Date of 1978 Amendment

Amendment by Pub. L. 95-633 effective on date the Convention on Psychotropic Substances enters into force in the United States [July 15, 1980], see section 112 of Pub. L. 95-633, set out as an Effective Date note under section 801a of this title.

Section 1308.01 Scope of Part 1308.

Schedules of controlled substances established by section 202 of the Act (**21 U.S.C. 812**), as they are changed, updated, and republished from time to time, are set forth in this part.

Section 1308.11 Schedule I.

(a) Schedule I shall consist of the drugs and other substances, by whatever official name, common or usual name, chemical name, or brand name designated, listed in this section. Each drug or substance has been assigned the DEA Controlled Substances Code Number set forth opposite it.

(b) Opiates. Unless specifically excepted or unless listed in another schedule, any of the following opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters and ethers, whenever the existence of such isomers, esters, ethers and salts is possible within the specific chemical designation (for purposes of paragraph **(b)(34)** only, the term isomer includes the optical and geometric isomers):

(1) Acetyl-alpha-methylfentanyl (N-[1-(1-methyl-2-phenethyl)-4-piperidinyl]-N-phenylacetamide)	9815
(2) Acetylmethadol	9601
(3) Allylprodine	9602
(4) Alphacetylmethadol (except levo-alphacetylmethadol also known as levo-alpha-acetylmethadol, levomethadyl acetate, or LAAM)	9603
(5) Alphameprodine	9604
(6) Alphamethadol	9605
(7) Alpha-methylfentanyl (N-[1-(alpha-methyl-beta-phenyl)ethyl-4-piperidyl] propionanilide; 1-(1-methyl-2-phenylethyl)-4-(N-propanilido) piperidine)	9814
(8) Alpha-methylthiofentanyl (N-[1-methyl-2-(2-thienyl)ethyl-4-piperidinyl]-N-phenylpropanamide)	9832
(9) Benzethidine	9606
(10) Betacetylmethadol	9607
(11) Beta-hydroxyfentanyl (N-[1-(2-hydroxy-2-phenethyl)-4-	9830

piperidinyl]-N-phenylpropanamide)	
(12) Beta-hydroxy-3-methylfentanyl (other name: N-[1-(2-hydroxy-2-phenethyl)-3-methyl-4-piperidinyl]-N-phenylpropanamide	9831
(13) Betameprodine	9608
(14) Betamethadol	9609
(15) Betaprodine	9611
(16) Clonitazene	9612
(17) Dextromoramide	9613
(18) Diampromide	9615
(19) Diethylthiambutene	9616
(20) Difenoxin	9168
(21) Dimenoxadol	9617
(22) Dimepheptanol	9618
(23) Dimethylthiambutene	9619
(24) Dioxaphetyl butyrate	9621
(25) Dipipanone	9622
(26) Ethylmethylthiambutene	9623
(27) Etonitazene	9624
(28) Etoxeridine	9625
(29) Furethidine	9626
(30) Hydroxypethidine	9627
(31) Ketobemidone	9628
(32) Levomoramide	9629
(33) Levophenacylmorphan	9631
(34) 3-Methylfentanyl (N-[3-methyl-1-(2-phenylethyl)-4-piperidyl]-N-phenylpropanamide)	9813
(35) 3-methylthiofentanyl (N-[(3-methyl-1-(2-thienyl)ethyl-4-piperidinyl]-N-phenylpropanamide)	9833
(36) Morpheridine	9632
(37) MPPP (1-methyl-4-phenyl-4-propionoxypiperidine)	9661
(38) Noracymethadol	9633
(39) Norlevorphanol	9634
(40) Normethadone	9635
(41) Norpipanone	9636
(42) Para-fluorofentanyl (N-(4-fluorophenyl)-N-[1-(2-phenethyl)-4-piperidinyl] propanamide	9812
(43) PEPAP (1-(-2-phenethyl)-4-phenyl-4-acetoxypiperidine	9663
(44) Phenadoxone	9637
(45) Phenampromide	9638

(46) Phenomorphan	9647
(47) Phenoperidine	9641
(48) Piritramide	9642
(49) Proheptazine	9643
(50) Properidine	9644
(51) Propiram	9649
(52) Racemoramide	9645
(53) Thiofentanyl (N-phenyl-N-[1-(2-thienyl)ethyl-4-piperidinyl]-propanamide	9835
(54) Tilidine	9750
(55) Trimeperidine	9646

(c) Opium derivatives. Unless specifically excepted or unless listed in another schedule, any of the following opium derivatives, its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation:

(1) Acetorphine	9319
(2) Acetyldihydrocodeine	9051
(3) Benzylmorphine	9052
(4) Codeine methylbromide	9070
(5) Codeine-N-Oxide	9053
(6) Cyprenorphine	9054
(7) Desomorphine	9055
(8) Dihydromorphine	9145
(9) Drotebanol	9335
(10) Etorphine (except hydrochloride salt)	9056
(11) Heroin	9200
(12) Hydromorphinol	9301
(13) Methyldesorphine	9302
(14) Methyldihydromorphine	9304
(15) Morphine methylbromide	9305
(16) Morphine methylsulfonate	9306
(17) Morphine-N-Oxide	9307
(18) Myrophine	9308
(19) Nicocodeine	9309
(20) Nicomorphine	9312
(21) Normorphine	9313
(22) Pholcodine	9314
(23) Thebacon	9315

(d) Hallucinogenic substances. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation, which contains any quantity of the following hallucinogenic substances, or which contains any of its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation (for purposes of this paragraph only, the term "isomer" includes the optical, position and geometric isomers):

(1) Alpha-ethyltryptamine	7249
Some trade or other names: etryptamine; Monase; alpha-ethyl-1H-indole-3-ethanamine; 3-(2-aminobutyl) indole; alpha-ET; and AET.	
(2) 4-bromo-2,5-dimethoxy-amphetamine	7391
Some trade or other names: 4-bromo-2,5-dimethoxy--alpha-methylphenethylamine; 4-bromo-2,5-DMA	
(3) 4-Bromo-2,5-dimethoxyphenethylamine	7392
Some trade or other names: 2-(4-bromo-2,5-dimethoxyphenyl)-1-aminoethane; alpha-desmethyl DOB; 2C-B, Nexus.	
(4) 2,5-dimethoxyamphetamine	7396
Some trade or other names: 2,5-dimethoxy-alpha-methylphenethylamine; 2,5-DMA	
(5) 2,5-dimethoxy-4-ethylamphet-amine	7399
Some trade or other names: DOET	
(6) 2,5-dimethoxy-4-(n)-propylthiopenenthylamine (2C-T-7), its optical isomers, salts and salts of isomers	7348
(7) 4-methoxyamphetamine	7411
Some trade or other names: 4-methoxy-alpha-methylphenethylamine; paramethoxyamphetamine, PMA	
(8) 5-methoxy-3,4-mdthylenedioxy-amphetamine	7401
(9) 4-methyl-2,5-dimethoxy-amphetamine	7395
Some trade and other names: 4-methyl-2,5-dimethoxy-alpha-methylphenethylamine; "DOM"; and "STP"	
(10) 3,4-methylenedioxy amphetamine	7400
(11) 3,4-methylenedioxymethamphetamine (MDMA)	7405
(12) 3,4-methylenedioxy-N-ethylamphetamine (also known as N-ethyl-alpha-methyl-3,4(methylenedioxy)phenethylamine, N-ethyl MDA, MDE, MDEA	7404
(13) N-hydroxy-3,4-methylenedioxyamphetamine (also known as N-hydroxy-alpha-methyl-3,4(methylenedioxy)phenethylamine, and N-hydroxy MDA	7402
(14) 3,4,5-trimethoxy amphetamine	7390
(15) Alpha-methyltryptamine (other name: AMT)	7432
(16) Bufotenine	7433
Some trade and other names: 3-(beta-Dimethylaminoethyl)-5-hydroxyindole; 3-	

(2-dimethylaminoethyl)-5-indolol; N, N-dimethylserotonin; 5-hydroxy-N,N-dimethyltryptamine; mappine	
(17) Diethyltryptamine	7434
Some trade and other names: N,N-Diethyltryptamine; DET	
(18) Dimethyltryptamine	7435
Some trade or other names: DMT	
(19) 5-methoxy-N,N-diisopropyltryptamine (5-MeO-DIPT), its isomers, salts and salts of isomers	7439
(20) Ibogaine	7260
Some trade and other names: 7-Ethyl-6,6 beta;,7,8,9,10,12,13-octahydro-2-methoxy-6,9-methano-5H-pyrido [1', 2':1,2] azepino [5,4-b] indole; Tabernanthe iboga	
(21) Lysergic acid diethylamide	7315
(22) Marihuana	7360
(23) Mescaline	7381
(24) Parahexyl--7374; some trade or other names: 3-Hexyl-1-hydroxy-7,8,9,10-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran; Synhexyl.	
(25) Peyote	7415
Meaning all parts of the plant presently classified botanically as Lophophora williamsii Lemaire, whether growing or not, the seeds thereof, any extract from any part of such plant, and every compound, manufacture, salts, derivative, mixture, or preparation of such plant, its seeds or extracts (Interprets 21 USC 812(c), Schedule I(c) (12))	
(26) N-ethyl-3-piperidyl benzilate	7482
(27) N-methyl-3-piperidyl benzilate	7484
(28) Psilocybin	7437
(29) Psilocyn	7438
(30) Tetrahydrocannabinols	7370
Meaning tetrahydrocannabinols naturally contained in a plant of the genus Cannabis (cannabis plant), as well as synthetic equivalents of the substances contained in the cannabis plant, or in the resinous extractives of such plant, and/or synthetic substances, derivatives, and their isomers with similar chemical structure and pharmacological activity to those substances contained in the plant, such as the following: -1 cis or trans tetrahydrocannabinol, and their optical isomers -6 cis or trans tetrahydrocannabinol, and their optical isomers -3,4 cis or trans tetrahydrocannabinol, and its optical isomers (Since nomenclature of these substances is not internationally standardized, compounds of these structures, regardless of numerical designation of atomic	

positions covered.)	
(31) Ethylamine analog of phencyclidine	7455
Some trade or other names: N-ethyl-1-phenylcyclohexylamine, (1-phenylcyclohexyl)ethylamine, N-(1-phenylcyclohexyl)ethylamine, cyclohexamine, PCE	
(32) Pyrrolidine analog of phencyclidine	7458
Some trade or other names: 1-(1-phenylcyclohexyl)-pyrrolidine, PCPy, PHP	
(33) Thiophene analog of phencyclidine	7470
Some trade or other names: 1-[1-(2-thienyl)-cyclohexyl]-piperidine, 2-thienylanalog of phencyclidine, TPCP, TCP	
(34) 1-[1-(2-thienyl)cyclohexyl]pyrrolidine	7473
Some other names: TCPy	

(e) Depressants. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a depressant effect on the central nervous system, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation:

(1) gamma-hydroxybutyric acid (some other names include GHB; gamma-hydroxybutyrate; 4-hydroxybutyrate; 4-hydroxybutanoic acid; sodium oxybate; sodium oxybutyrate)	2010
(2) Mecloqualone	2572
(3) Methaqualone	2565

(f) Stimulants. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a stimulant effect on the central nervous system, including its salts, isomers, and salts of isomers:

(1) Aminorex (Some other names: aminoxaphen; 2-amino-5-phenyl-2- oxazoline; or 4,5-dihydro-5-phenly-2-oxazolamine)	1585
(2) N-benzylpiperazine (some other names: BZP; 1-benzylpiperazine), its optical isomers, salts and salts of isomers	7493
(3) Cathinone	1235
Some trade or other names: 2-amino-1-phenyl-1-propanone, alpha-aminopropiophenone, 2-aminopropiophenone, and norephedrone	
(4) Fenethylline	1503
(5) Methcathinone (Some other names: 2-(methylamino)-propiophenone; alpha-(methylamino)propiophenone; 2-(methylamino)-1-phenylpropan-1-one; alpha-N-methylaminopropiophenone; monomethylpropion; ephedrone; N-methylcathinone; methylcathinone; AL-464; AL-422; AL-463 and UR1432), its salts, optical isomers and salts of optical	1237

isomers	
(6) (+/-)cis-4-methylaminorex ((+/-)cis-4,5-dihydro-4-methyl-5-phenyl-2-oxazolamine)	1590
(7) N-ethylamphetamine	1475
(8) N,N-dimethylamphetamine (also known as N,N-alpha-trimethyl-benzeneethanamine; N,N-alpha-trimethylphenethylamine)	1480

(g) *Temporary listing of substances subject to emergency scheduling.* Any material, compound, mixture or preparation which contains any quantity of the following substances:

(1) [Reserved]

(2) [Reserved]

[39 FR 22141, June 20, 1974]

Editorial Note: For federal Register citations affecting 1308.11, see the List of CFR Sections Affected, which appears in the Finding Aids section of the printed volume and on GPO Access.

Effective Date Note: At 68 FR 14119, Mar. 21, 2003, Section 1308.11 was amended by revising paragraph (d)(27), effective April 21, 2003.

Section 1308.12 Schedule II.

(a) Schedule II shall consist of the drugs and other substances, by whatever official name, common or usual name, chemical name, or brand name designated, listed in this section. Each drug or substance has been assigned the Controlled Substances Code Number set forth opposite it.

(b) Substances, vegetable origin or chemical synthesis. Unless specifically excepted or unless listed in another schedule, any of the following substances whether produced directly or indirectly by extraction from substances of vegetable origin, or independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis:

(1) Opium and opiate, and any salt, compound, derivative, or preparation of opium or opiate excluding apomorphine, thebaine-derived butorphanol, dextrorphan, nalbuphine, nalmefene, naloxone, and naltrexone, and their respective salts, but including the following:

(i) Codeine	9050
(ii) Dihydroetorphine	9334
(iii) Ethylmorphine	9190
(iv) Etorphine hydrochloride	9059
(v) Granulated opium	9640

(vi) Hydrocodone	9193
(vii) Hydromorphone	9150
(viii) Metopon	9260
(ix) Morphine	9300
(x) Opium extracts	9610
(xi) Opium fluid	9620
(xii) Oripavine	9330
(xiii) Oxycodone	9143
(xiv) Oxymorphone	9652
(xv) Powdered opium	9639
(xvi) Raw opium	9600
(xvii) Thebaine	9333
(xviii) Tincture of opium	9630

(2) Any salt, compound, derivative, or preparation thereof which is chemically equivalent or identical with any of the substances referred to in **paragraph (b) (1)** of this section, except that these substances shall not include the isoquinoline alkaloids of opium.

(3) Opium poppy and poppy straw.

(4) Coca leaves (9040) and any salt, compound, derivative or preparation of coca leaves (including cocaine (9041) and ecgonine (9180) and their salts, isomers, derivatives and salts of isomers and derivatives), and any salt, compound, derivative, or preparation thereof which is chemically equivalent or identical with any of these substances, except that the substances shall not include decocainized coca leaves or extraction of coca leaves, whhch extractions do not contain cocaine or ecgonine.

(5) Concentrate of poppy straw (the crude extract of poppy straw in either liquid, solid or powder form which contains the phenanthrene alkaloids of the opium poppy), 9670.

(c) Opiates. Unless specifically excepted or unless in another schedule any of the following opiates, including its isomers, esters, ethers, salts and salts of isomers, esters and ethers whenever the existence of such isomers, esters, ethers, and salts is possible within the specific chemical designation, dextrorphan and levopropoxyphene excepted:

(1) Alfentanil	9737
(2) Alphaprodine	9010
(3) Anileridine	9020
(4) Bezitramide	9800
(5) Bulk dextropropoxyphene (non-dosage forms)	9273
(6) Carfentanil	9743
(7) Dihydrocodeine	9120
(8) Diphenoxylate	9170
(9) Fentanyl	9801
(10) Isomethadone	9226

(11) Levo-alphacetylmethadol [Some other names: levo-alpha-acetylmethadol, levomethadyl acetate, LAAM]	9648
(12) Levomethorphan	9210
(13) Levorphanol	9220
(14) Metazocine	9240
(15) Methadone	9250
(16) Methadone-Intermediate, 4-cyano-2-dimethylamino-4,4-diphenyl butane	9254
(17) Moramide-Intermediate, 2-methyl-3-morpholino-1, 1-diphenylpropane-carboxylic acid	9802
(18) Pethidine (meperidine)	9230
(19) Pethidine-Intermediate-A, 4-cyano-1-methyl-4-phenylpiperidine	9232
(20) Pethidine-Intermediate-B, ethyl-4-phenylpiperidine-4-carboxylate	9233
(21) Pethidine-Intermediate-C, 1-methyl-4-phenylpiperidine-4-carboxylic acid	9234
(22) Phenazocine	9715
(23) Piminodine	9730
(24) Racemethorphan	9732
(25) Racemorphan	9733
(26) Remifentanil	9739
(27) Sufentanil	9740
(28) Tapentadol	9780

(d) Stimulants. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a stimulant effect on the central nervous system:

(1) Amphetamine, its salts, optical isomers, and salts of its optical isomers	1100
(2) Methamphetamine, its salts, isomers, and salts of its isomers	1105
(3) Phenmetrazine and its salts	1631
(4) Methylphenidate	1724
(5) Lisdexamfetamine, its salts, isomers, and salts of its isomers	1205

(e) Depressants. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a depressant effect on the central nervous system, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation:

(1) Amobarbital	2125
(2) Glutethimide	2550

(3) Pentobarbital	2270
(4) Phencyclidine	7471
(5) Secobarbital	2315

(f) Hallucinogenic substances.

(1) Nabilone	7379
[Another name for nabilone: (+/-)-trans-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6, 6-dimethyl-9H-dibenzo[b,d]pyran-9-one]	

(g) Immediate precursors. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances:

(1) Immediate precursor to amphetamine and methamphetamine:

(i) Phenylacetone	8501
Some trade or other names: phenyl-2-propanone; P2P; benzyl methyl ketone; methyl benzyl ketone;	

(2) Immediate precursors to phencyclidine (PCP):

(i) 1-phenylcyclohexylamine	7460
(ii) 1-piperidinocyclohexanecarbonitrile (PCC)	8603

[39 FR 22142, June 20, 1974]

Editorial Note: ForFederal Registercitations affecting §1308.12, see the List of CFR Sections Affected, which appears in the Finding Aids section of the printed volume and on GPO Access.

Section 1308.13 Schedule III.

(a) Schedule III shall consist of the drugs and other substances, by whatever official name, common or usual name, chemical name, or brand name designated, listed in this section. Each drug or substance has been assigned the DEA Controlled Substances Code Number set forth opposite it.

(b) Stimulants. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a stimulant effect on the central nervous sxstem, including its salts, isomers (whether optical, position, or geometric), and salts of such isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation:

(1) Those compounds, mixtures, or preparations in dosage unit form containing any stimulant substances listed in schedule II	1405

which compounds, mixtures, or preparations were listed on August 25, 1971, as excepted compounds under **Sec. 1308.32**, and any other drug of the quantitative composition shown in that list for those drugs or which is the same except that it contains a lesser quantity of controlled substances	
(2) Benzphetamine	1228
(3) Chlorphentermine	1645
(4) Clortermine	1647
(5) Phendimetrazine	1615

(c) Depressants. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a depressant effect on the central nervous system:

(1) Any compound, mixture or preparation containing: (i) Amobarbital 2126 (ii) Secobarbital 2316 (iii) Pentobarbital 2271 or any salt thereof and one or more other active medicinal ingredients which are not listed in any schedule.	
(2) Any suppository dosage form containing: (i) Amobarbital 2126 (ii) Secobarbital 2316 (iii) Pentobarbital 2271 or any salt of any of these drugs and approved by the Food and Drug Administration for marketing only as a suppository.	
(3) Any substance which contains any quantity of a derivative of barbituric acid or any salt thereof	2100
(4) Chlorhexadol	2510
(5) Embutramide	2020
(6) Any drug product containing gamma hydroxybutyric acid, including its salts, isomers, and salts of isomers, for which an application is approved under section 505 of the Federal Food, Drug, and Cosmetic Act	2012
(7) Ketamine, its salts, isomers, and salts of isomers	7285
[Some other names for ketamine: (±)-2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone]	

(8) Lysergic acid	7300
(9) Lysergic acid amide	7310
(10) Methyprylon	2575
(12) Sulfondiethylmethane	2600
(13) Sulfonethylmethane	2605
(13) Sulfonmethane	2610
(14) Tiletamine and zolazepam or any salt thereof	7295
Some trade or other names for a tiletamine-zolazepam combination product: Telazol Some trade or other names for tiletamine: 2-(ethylamino)-2-(2-thienyl)-cyclohexanone Some trade or other names for zolazepam: 4-(2-fluorophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo-[3,4-e] [1,4]-diazepin-7(1H)-one, flupyrazapon	

(d) Nalorphine 9400.

(e) Narcotic Drugs. Unless specifically excepted or unless listed in another schedule:

(1) Any material, compound, mixture, or preparation containing any of the following narcotic drugs, or their salts calculated as the free anhydrous base or alkaloid, in limited quantities as set forth below:

(i) Not more than 1.8 grams of codeine per 100 milliliters or not more than 90 milligrams per dosage unit, with an equal or greater quantity of an isoquinoline alkaloid of opium	9803
(ii) Not more than 1.8 grams of codeine per 100 milliliters or not more than 90 milligrams per dosage unit, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts	9804
(iii) Not more than 300 milligrams of dihydrocodeinone (hydrocodone) per 100 milliliters or not more than 15 milligrams per dosage unit, with a fourfold or greater quantity of an isoquinoline alkaloid of opium	9805
(iv) Not more than 300 milligrams of dihydrocodeinone (hydrocodone) per 100 milliliters or not more than 15 milligrams per dosage unit, with one or more active nonnarcotic ingredients in recognized therapeutic amounts	9806
(v) Not more than 1.8 grams of dihydrocodeine per 100 milliliters or not more than 90 milligrams per dosage unit, with one or more active nonnarcotic ingredients in recognized therapeutic amounts	9807
(vi) Not more than 300 milligrams of ethylmorphine per 100	9808

milliliters or not more than 15 milligrams per dosage unit, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts	
(vii) Not more than 500 milligrams of opium per 100 milliliters or per 100 grams or not more than 25 milligrams per dosage unit, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts	9809
(viii) Not more than 50 milligrams of morphine per 100 milliliters or per 100 grams, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts	9810

(2) Any material, compound, mixture, or preparation containing any of the following narcotic drugs or their salts, as set forth below:

(i) Buprenorphine (ii) [Reserved]	9064

(f) Anabolic Steroids. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture or preparation containing any quantity of the following substances, including its salts, esters and ethers:

(1) Anabolic steroids (see Sec. 1300.01 of this chapter)	4000
(2) [Reserved]	

(g) Hallucinogenic substances.

(1) Dronabinol (synthetic) in sesame oil and encapsulated in a soft gelatin capsule in a U.S. Food and Drug Administration approved product	7369
[Some other names for dronabinol: (6a*R-trans*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo [*b,d*]pyran-1-ol] or (-)-delta-9-(*trans*)-tetrahydrocannabinol]	

[39 FR 22142, June 20, 1974, as amended at 41 FR 43401, Oct. 1, 1976; 43 FR 3359, Jan. 25, 1978; 44 FR 40888, July 13, l979; 46 FR 52334, Oct. 27, 1981; 51 FR 5320, Feb. 13, 1986; 52 FR 2222, Jan. 21, 1987; 52 FR 5952, Feb. 27, 1987; 56 FR 5754, Feb. 13, 1991; 56 FR 11932, Mar. 21, 1991; 62 FR 13968, Mar. 24, 1997; 64 FR 35930, July 2, 1999; 64 FR 37675, July 13, 1999; 65 FR 13238 Mar. 13, 2000; 65 FR 17440, Apr. 3, 2000; 67 FR 62370, Oct. 7, 2002; 70 FR 74657, Dec. 16, 2005; 71 FR 51116, Aug 29, 2006]

Section 1308.14 Schedule IV.

(a) Schedule IV shall consist of the drugs and other substances, by whatever official name, common or usual name, chemical name, or brand name designated, listed in this

section. Each drug or substance has been assigned the DEA Controlled Substances Code Number set forth opposite it.

(b) Narcotic drugs. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation containing any of the following narcotic drugs, or their salts calculated as the free anhydrous base or alkaloid, in limited quantities as set forth below:

(1) Not more than 1 milligram of difenoxin and not less than 25 micrograms of atropine sulfate per dosage unit	9167
(2) Dextropropoxyphene (alpha-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane)	9278

(c) Depressants. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation:

(1) Alprazolam	2882
(2) Barbital	2145
(3) Bromazepam	2748
(4) Camazepam	2749
(5) Chloral betaine	2460
(6) Chloral hydrate	2465
(7) Chlordiazepoxide	2744
(8) Clobazam	2751
(9) Clonazepam	2737
(10) Clorazepate	2768
(11) Clotiazepam	2752
(12) Cloxazolam	2753
(13) Delorazepam	2754
(14) Diazepam	2765
(15) Dichloraphenazone	2467
(16) Estazolam	2756
(17) Ethchlorvynol	2540
(18) Ethinamate	2545

(19) Ethyl loflazepate	2758
(20) Fludiazepam	2759
(21) Flunitrazepam	2763
(22) Flurazepam	2767
(23) Fospropofol	2138
(24) Halazepam	2762
(25) Haloxazolam	2771
(26) Ketazolam	2772
(27) Loprazolam	2773
(28) Lorazepam	2885
(29) Lormetazepam	2774
(30) Mebutamate	2800
(31) Medazepam	2836
(32) Meprobamate	2820
(33) Methohexital	2264
(34) Methylphenobarbital (mephobarbital)	2250
(35) Midazolam	2884
(36) Nimetazepam	2837
(37) Nitrazepam	2834
(38) Nordiazepam	2838
(39) Oxazepam	2835
(40) Oxazolam	2839
(41) Paraldehyde	2585
(42) Petrichloral	2591
(43) Phenobarbital	2285
(44) Pinazepam	2883
(45) Prazepam	2764
(46) Quazepam	2881
(47) Temazepam	2925
(48) Tetrazepam	2886
(49) Triazolam	2887
(50) Zaleplon	2781
(51) Zolpidem	2783
(52) Zopiclone	2784

(d) Fenfluramine. Any material, compound, mixture, or preparation which contains any quantity of the following substances, including its salts, isomers (whether optical, position, or geometric), and salts of such isomers, whenever the existence of such salts, isomers, and salts of isomers is possible:

(1) Fenfluramine	1670

(e) Stimulants. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a stimulant effect on the central nervous system, including its salts, isomers and salts of isomers:

(1) Cathine ((+)-norpseudoephedrine)	1230
(2) Diethylpropion	1610
(3) Fencamfamin	1760
(4) Fenproporex	1575
(5) Mazindol	1605
(6) Mefenorex	1580
(7) Modafinil	1680
(8) Pemoline (including organometallic complexes and chelates thereof)	1530
(9) Phentermine	1640
(10) Pipradrol	1750
(11) Sibutramine	1675
(12) SPA ((-)-1-dimethylamino- 1,2-diphenylethane)	1635

(f) Other substances. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture or preparation which contains any quantity of the following substances, including its salts:

(1) Pentazocine	9709
(2) Butorphanol (including its optical isomers)	9720

[39 FR 22143, June 20, 1974]

Section 1308.15 Schedule V.

(a) Schedule V shall consist of the drugs and other substances, by whatever official name, common or usual name, chemical name, or brand name designated, listed in this section.

(b) *Narcotic drugs*. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation containing any of the following narcotic drugs and their salts, as set forth below:

(1) [Reserved]

* * * * *

(c) *Narcotic drugs containing non-narcotic active medicinal ingredients.* Any compound, mixture, or preparation containing any of the following narcotic drugs, or their salts calculated as the free anhydrous base or alkaloid, in limited quantities as set forth below, which shall include one or more non-narcotic active medicinal ingredients in sufficient proportion to confer upon the compound, mixture, or preparation valuable medicinal qualities other than those possessed by narcotic drugs alone:

(1) Not more than 200 milligrams of codeine per 100 milliliters or per 100 grams.

(2) Not more than 100 milligrams of dihydrocodeine per 100 milliliters or per 100 grams.

(3) Not more than 100 milligrams of ethylmorphine per 100 milliliters or per 100 grams.

(4) Not more than 2.5 milligrams of diphenoxylate and not less than 25 micrograms of atropine sulfate per dosage unit.

(5) Not more than 100 milligrams of opium per 100 milliliters or per 100 grams.

(6) Not more than 0.5 milligram of difenoxin and not less than 25 micrograms of atropine sulfate per dosage unit.

(d) *Stimulants.* Unless specifically exempted or excluded or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a stimulant effect on the central nervous system, including its salts, isomers and salts of isomers:

(1) Pyrovalerone	1485
(2) [Reserved]	

(e) *Depressants.* Unless specifically exempted or excluded or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a depressant effect on the central nervous system, including its salts:

(1) Lacosamide [(*R*)-2-acetoamido- *N* -benzyl-3-methoxy-propionamide]—2746

(2) Pregabalin [(S)-3-(aminomethyl)-5-methylhexanoic acid]—2782

[39 FR 22143, June 20, 1974, as amended at 43 FR 38383, Aug. 28, 1978; 44 FR 40888, July 13, 1979; 47 FR 49841, Nov. 3, 1982; 50 FR 8108, Feb. 28, 1985; 52 FR 5952, Feb. 27, 1987; 53 FR 10870, Apr. 4, 1988; 56 FR 61372, Dec. 3, 1991; 67 FR 62370, Oct. 7, 2002; 70 FR 43635, July 28, 2005; 74 FR 23790, May 21, 2009]

EXCLUDED NONNARCOTIC SUBSTANCES

Section 1308.21 Application for exclusion of a nonnarcotic substance.

(a) Any person seeking to have any nonnarcotic drug that may, under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301), be lawfully sold over the counter without a prescription, excluded from any schedule, pursuant to section 201(g)(1) of the Act (**21 U.S.C. 811**(g)(1)), may apply to the Office of Diversion Control, Drug Enforcement Administration. See the Table of DEA Mailing Addresses in **Sec. 1321.01** of this chapter for the current mailing address.

(b) An application for an exclusion under this section shall contain the following information:

(1) The name and address of the applicant;

(2) The name of the substance for which exclusion is sought; and

(3) The complete quantitative composition of the substance.

(c) Within a reasonable period of time after the receipt of an application for an exclusion under this section, the Administrator shall notify the applicant of his acceptance or nonacceptance of his application, and if not accepted, the reason therefore. The Administrator need not accept an application for filing if any of the requirements prescribed in **paragraph (b)** of this section is lacking or is not set forth as to be readily understood. If the applicant desires, he may amend the application to meet the requirements of **paragraph (b)** of this section. If the application is accepted for filing, the Administrator shall issue and publish in the Federal Register his order on the application, which shall include a reference to the legal authority under which the order is issued and the findings of fact and conclusions of law upon which the order is based. This order shall specify the date on which it shall take effect. The Administrator shall permit any interested person to file written comments on or objections to the order within 60 days of the date of publication of his order in the Federal Register. If any such comments or objections raise significant issues regarding any finding of fact or conclusion of law upon which the order is based, the Administrator shall immediately suspend the effectiveness of the order until he may reconsider the application in light of the comments and objections filed. Thereafter, the Administrator shall reinstate, revoke, or amend his original order as he determines appropriate.

(d) The Administrator may at any time revoke any exclusion granted pursuant to section 201(g) of the Act (**21 U.S.C. 811(g)**) by following the procedures set forth in **paragraph (c)** of this section for handling an application for an exclusion which has been accepted for filing.

[38 FR 8254, Mar. 30, 1973, as amended at 70 FR 74657, Dec. 16, 2005, 75 FR 10678, Mar. 9, 2010]

Section 1308.22 Excluded substances.

The following nonnarcotic substances which may, under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301), be lawfully sold over the counter without a prescription, are excluded from all schedules pursuant to section 201(g) (1) of the Act (**21 U.S.C. 811(g)(1)**):

Excluded Nonnarcotic Products

Company	Trade Name	NDC Code	Form	Controlled Substance	(mg or mg/ml)
Bioline Laboratories	Theophed	00719-1945	TB	Phenobarbital	8.00
Classic Pharmaceuticals LLC	Nasal Decongestant Inhaler/Vapor Inhaler		IN	Levmetamfetamine (l-Desoxyephedrin e)	50.00
Goldline Laboratories	Guiaphed Elixir	00182-1377	EL	Phenobarbital	4.00
Goldline Laboratories	Tedrigen Tablets	00182-0134	TB	Phenobarbital	8.00
Hawthorne Products Inc	Choate's Leg Freeze		LQ	Chloral hydrate	246.67
Parke-Davis & Co	Tedral	00071-0230	TB	Phenobarbital	8.00
Parke-Davis & Co	Tedral Elixir	00071-0242	EX	Phenobarbital	40.00
Parke-Davis & Co	Tedral S.A.	00071-0231	TB	Phenobarbital	8.00
Parke-Davis & Co	Tedral Suspension	00071-0237	SU	Phenobarbital	80.00
Parmed Pharmacy	Asma-Ese	00349-2018	TB	Phenobarbital	8.10
Rondex Labs	Azma-Aids	00367-3153	TB	Phenobarbital	8.00
Smith Kline Consumer	Benzedrex	49692-0928	IN	Propylhexedrine	250.00
Sterling Drug, Inc	Bronkolixir	00057-1004	EL	Phenobarbital	0.80
Sterling Drug, Inc	Bronkotabs	00057-1005	TB	Phenobarbital	8.00
Vicks Chemical Co	Vicks Inhaler	23900-0010	IN	I-Desoxyephedrine	113.00
White Hall Labs	Primatene (P-tablets)	00573-2940	TB	Phenobarbital	8.00

[38 FR 8255, Mar. 30, 1973. Redesignated at 38 FR 26609, Sept. 24, l973, and amended at 41 FR 16553, Apr. 20, 1976; 41 FR 53477, Dec. 7, 1976; 46 FR 51603, Oct. 21, 1981; 47 FR 45867, Oct. 14, 1982; 54 FR 2100, Jan. 19, 1989; 55 FR 12162, Mar. 30, 1990; 62 FR 13968, Mar. 24, 1997;74 FR 44283, Aug. 28, 2009]

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 14, 2010

From: Division of Nonprescription Regulation Development

Through: Office Drug Evaluation IV

To: Members of the Drug Safety and Risk Management Committee, Consultants and Guests

Subject: FDA Discussion of Abuse Potential of the Drug Dextromethorphan

This memo provides information about how FDA evaluates the safety and efficacy of nonprescription drugs and the regulatory background history of dextromethorphan containing products for over-the-counter (OTC) use.

A. *How does FDA evaluate nonprescription drug products?*
The safety and efficacy of OTC (i.e., nonprescription) drugs are evaluated by one of two mechanisms: the New Drug Application (NDA) process or the OTC Drug Review (OTC Monograph system).

NDA Process
The NDA review process was established with the publication of the 1938 Federal Food Drug and Cosmetic Act (the Act) which required that all new drugs introduced after 1938 be proven safe for human use prior to marketing. The Act was amended in 1962 to require that all drug products (both prescription and OTC) be shown safe and effective for their intended use prior to marketing. These very same standards (i.e., safety and efficacy) apply today for all drug products marketed under an NDA. The NDA review process is confidential, and approval may result in a period of marketing exclusivity. In addition, once approved there are stringent post-marketing reporting requirements that include adverse event reporting and the submission of any information that may have a bearing on the safe and effective use of the drug.

OTC Drug Review (Monograph)
At the time of passage of the 1962 Drug Amendments Act, there were approximately 300,000 OTC drug products on the market. Of those 300,000 OTC drug products, only an estimated 500 were approved for marketing under an NDA as safe and of those only 25 percent were found to be effective for one or more of their intended uses. Thus, an extensive review of all OTC drugs was initiated on May 11, 1972, to determine their safety and effectiveness. The review only included OTC products that were marketed in

the United States prior to the 1972 initiation date. This date was subsequently extended to December 4, 1975.

The review was conducted by expert review panels, consisting of healthcare practitioners and scientists (similar to today's Advisory Committee) to review the various therapeutic categories. In total there were up to 80 or more categories that ranged from acne drug products to weight control drug products. Within each therapeutic category, the panels looked at the active ingredients rather than the individual drug products. There were approximately 800 significant active ingredients. The active ingredients reviewed by the panel were classified in one of three ways:

Category	Description
Category I	Generally recognized as safe and effective and not misbranded (GRASE)
Category II	Not generally recognized as safe and effective or is misbranded (Not GRASE)
Category III	Insufficient data available to permit classification. Allows a manufacturer an opportunity to show that the ingredients in a product are effective, and, if they are not, to reformulate or appropriately re-label the product

After extensive reviews and deliberations, the expert review panels made recommendations to FDA of their findings in a form of a panel report for each therapeutic category. These panel reports were published in the Federal Register as an Advanced Notice of Proposed Rulemaking (ANPR). The publication of the ANPR begins the multistep public notice and comment rulemaking process as shown below.

OTC Drug Review Step	Process
Expert Advisory Review Panel Evaluation	Evaluation of data submitted in response to FDA's call for data on an OTC drug product category (e.g., cough/cold drug products). Panel deliberations are public.
Advance Notice of Proposed Rulemaking (ANPR)	Publication of the panel's recommendations based on these recommendations with an opportunity for comment and submission of new data
Tentative Final Monograph (TFM)	FDA's proposed regulation based on an evaluation of the panel's recommendations, public comments received in response to the ANPR, and any other new data received. After publication of the TFM, there is an additional opportunity for public comment and submission of new data.

Final Monograph (FM)	FDA's final regulation

The end product of the OTC Drug Review is a final regulation that describes active ingredients, their dose, and labeling conditions that are generally recognized as safe and effective for a specific OTC use. Some final rules also include final formulation testing requirements and protocols to demonstrate the effectiveness of specific product formulations. Drug products that are compliant with a final regulation may be marketed without prior FDA approval.

Unlike drugs approved through the NDA process, drug products regulated by the monograph process may continue to be marketed while undergoing evaluation by the panel and during the rulemaking process. However, this marketing is subject to the risk that some aspect of the drug product (e.g., active ingredient, dose, or labeling) might not be found as GRASE and thus could no longer be marketed with these conditions. Another notable difference between the two mechanisms is that the NDA process is strictly confidential where as the OTC Drug Review is accomplished through the multistep public notice and comment rulemaking. Also, no marketing exclusivity is conferred under the OTC Drug Review.

B. What is the regulatory background of OTC Dextromethorphan?

Dextromethorphan is a substance that is chemically related to codeine, though it is not an opiate. Currently there are over 100 OTC cough and cold drug products containing dextromethorphan available, either as single-entity products or in combination with other active ingredients. These products are available in the following immediate release dosage forms marketed under the OTC monograph system: suspensions, capsules or tablets as. It is also available in extended-release dosage forms marketed under the NDA approval process.

Overview of Dextromethorphan Antitussive Rulemakings

Advance Notice of Proposed Rulemaking (ANPR)
On September 9, 1976, FDA published an ANPR titled Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use ANPR (41 FR 38312). This initial rulemaking highlighted the findings from the cough and cold advisory review panel on the acceptability of dextromethorphan as an over-the-counter drug product.

The panel concluded that dextromethorphan is a "nonnarcotic antitussive agent…by selective suppression of the central cough mechanism and [has] no significant abuse liability." The panel classified dextromethorphan and dextromethorphan hydrobromide as Category I (GRASE) active ingredients.

Tentative Final Monograph (TFM)
On October 19, 1983, FDA published a TFM for Antitussive Drug Products (48 FR 48576) proposing that dextromethorphan and dextromethorphan hydrobromide as Category I antitussive active ingredients with labeling and directions for use based on the panel's recommendations.

In that TFM, FDA noted that from the ANPR "…dextromethorphan has a wide margin of safety with respect to its potential to cause poisoning through accidental overdose…no fatalities have been reported even with doses in excess of 100 times the normal adult dose...." FDA further noted that adverse reactions such as hallucinations, urticaria, nausea, insomnia, and hysteria had been reported but there were no reports of fatalities. The FDA concurred with the panel's findings and stated that with the "…low order of toxicity, dextromethorphan is probably the safest antitussive presently available."

Final Monograph (FM)
On August 12, 1987, FDA published the FM for Antitussive Drug Products (52 FR 30042) under which dextromethorphan is currently regulated for adults and children over 2 years of age.

C. What was discussed at prior Advisory Committee Meetings on dextromethorphan abuse?

Since the publication of the FM on Antitussive Drug Products, there has been an increase in reports of dextromethorphan abuse, especially by teenagers. In response to a citizen petition, two FDA advisory committee meetings were held that specifically focused on the issue of dextromethorphan abuse by teenagers. The following is a brief summary of the advisory committee meetings proceedings:

August 6-7, 1990, Drug Abuse Advisory Committee Meeting (55 FR 29671)
In 1990, an advisory committee was convened by the FDA in response to petitions to Pennsylvania and to Utah. These petitions dealt with reports of abuse of dextromethorphan-containing cough syrups by teenagers. The committee was asked to:

1. Help FDA identify and better define the extent of the problem
2. Develop a strategy for assessing the problem
3. Identify and discuss the pros and cons of possible solutions that can be applied

Invited speakers gave presentations and presented data on the nature of the problem, areas affected, the characteristics of those local areas, and information regarding the drug or the manner in which it is being used that made it a problem. FDA identified one commercial product, which contained dextromethorphan. The Drug Abuse Advisory Committee recommended that the sponsor of this product provide additional data on the toxicity of the substance in the higher dose range, and that additional epidemiological data be gathered so that FDA could better assess the scope and significance of the abuse and the risk to the public health.

July 14 and 15, 1992, Drug Abuse Advisory Committee Meeting (57 FR 27982)
In response to the recommendations of the Committee in 1990, one of the manufacturer's of the dextromethorphan-containing product submitted to FDA a series of studies they conducted and that they proposed to be conducted. FDA divided the review responsibilities for these study submissions to members of the Drug Abuse Advisory Committee. These members made presentations of their review of the submitted information. The sponsor proposed four research studies on dextromethorphan abuse:

1. A national survey of communities to include interviews with drug-free school coordinators
2. An assessment of the natural history of dextromethorphan abuse

3. A study to provide information on whether the degree of attention the abuse problem receives in a community is related to the rate at which students report using the drug
4. A study to evaluate the effect of a program designed to affect the attitudes and behavior of potential and actual dextromethorphan abusers

At the close of the meeting, there was no clear consensus of the extent of the problem or what actions should be taken to control it. In addition, FDA commented to the sponsor(s) that further studies are needed, and should focus on areas where abuse outbreaks are occurring. FDA also encouraged clinical investigators to collect clinical behavioral pharmacology data as part of future clinical studies using high dose dextromethorphan.

D. What is proposed to be discussed at the current Advisory Committee meeting i.e. September 14, 2010)

In a letter dated September 19, 2007, the Drug Enforcement Agency (DEA) expressed concern about increased incidence of dextromethorphan abuse, especially among adolescents. The letter formally requested that Department of Health and Human Services (DHHS), under the provisions of 21 U.S.C. § 811(b), conduct a scientific and medical evaluation and scheduling recommendation for dextromethorphan. Along with this request, DEA provided a document in the form of an eight-factor analysis containing their review of available data regarding dextromethorphan.

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Active Ingredient Search Results from "OB_Rx" table for query on "dextromethorphan."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
A088762	AA	Yes	DEXTROMETHORPHAN HYDROBROMIDE; PROMETHAZINE HYDROCHLORIDE	SYRUP; ORAL	15MG/5ML;6.25MG/5ML	PROMETH W/ DEXTROMETHORPHAN	ACTAVIS MID ATLANTIC
A040027	AA	No	DEXTROMETHORPHAN HYDROBROMIDE; PROMETHAZINE HYDROCHLORIDE	SYRUP; ORAL	15MG/5ML;6.25MG/5ML	PROMETHAZINE HYDROCHLORIDE AND DEXTROMETHORPHAN HYDROBROMIDE	HI TECH PHARMA
A040649	AA	No	DEXTROMETHORPHAN HYDROBROMIDE; PROMETHAZINE HYDROCHLORIDE	SYRUP; ORAL	15MG/5ML;6.25MG/5ML	PROMETHAZINE DM	VINTAGE
A088864	AA	No	DEXTROMETHORPHAN HYDROBROMIDE; PROMETHAZINE HYDROCHLORIDE	SYRUP; ORAL	15MG/5ML;6.25MG/5ML	PROMETHAZINE W/ DEXTROMETHORPHAN	WOCKHARDT

Abuse-Related Pharmacology of Dextromethorphan

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Abuse-Related Pharmacology of Dextromethorphan

Dextromethorphan (DXM) has been investigated for its abuse potential in animal studies, human studies and through evaluation of human epidemiological databases and case reports. The Controlled Substance Staff (CSS) at FDA has not received or evaluated any primary preclinical or clinical data regarding the abuse potential assessment of DXM. Thus, the CSS background paper relies on publicly-available information found in the scientific and medical literature. This information includes data from well-conducted studies, as well as from anecdotal case reports.

Preclinical Studies with Dextromethorphan

Chemistry

DXM is the methylated dextrorotatory analog of the synthetic Schedule II opioid, levorphanol, a derivative of codeine (Bem and Peck, 1992). Levorphanol can also be converted to the Schedule II opioids, racemethorphan and levomethorphan, the racemic and levorotatory forms of DXM (Banken and Foster, 2008).

Receptor Binding Studies with DXM

Binding of DXM to Mu-Opioid Receptors

Even though DXM is derived from opiate drugs, it has no significant affinity for mu-opioid receptors (Pert and Snyder, 1973). Dextrorotatory drugs typically do not have high affinity for the mu-opioid receptor, unlike levorotatory and racemic drugs (Pasternak, 1988). In contrast, opioids that are structurally similar to DXM, such as levorphanol, levomethorphan and racemethorphan, have high affinity at the mu opioid site.

Binding of DXM to NMDA Receptor Sites

In receptor binding studies, DXM binds with moderate to low affinity (Ki = 510 nM to IC50 =2.5 uM) at the phencyclidine "PCP site" of the NMDA receptor-channel (Murray and Leid, 1984). At that site, DXM acts as a noncompetitive NMDA receptor antagonist (Church et al., 1989; Franklin and Murray, 1992). This is thought to be the primary mechanism of action of DXM.

Binding of DXM to Other Central Nervous System Sites

In addition to the NMDA site, DXM binds to four other sites in the central nervous system:

- At sigma-1 receptor sites, DXM acts as a high-affinity agonist (Ki = 50-142 nM) (Zhou and Musacchio, 1991).

- At the voltage-dependent calcium channel, DXM induces inhibition of neurotransmission, creating a functional antagonism (Netzer et al., 1993; Carpenter et al., 1988).

- At the serotonin transporter, DXM binds with high affinity (Meoni et al., 1997), producing serotonin reuptake inhibitory activity (Henderson and Fuller, 1992; Gillman, 2005).

- At nicotinergic acetylcholine receptors, DXM is an antagonist (Damaj et al., 2005; Hernandez et al., 2000).

Preclinical Behavioral Studies with Dextromethorphan

General Behavioral Pharmacology Studies

In an evaluation of general behavioral pharmacological effects, DXM (60-100 mg/kg, i.p.) produced stereotypy that was similar to that produced by the NMDA antagonists, PCP (Schedule II) and ketamine (Schedule III) (Ishmael et al., 1998). Stereotypy is characterized by repetitive motor behaviors in an animal, such as pacing in a cage or continuous licking or biting.

DXM (15-120 mg/kg, i.p.) has also been shown to produce hyperactivity that is similar to that of PCP (Schedule II) (Szekely et al., 1991). Hyperactivity is characterized by an increase in locomotor behavior (that is, running around a cage) compared to normal resting behavior.

Self-Administration Studies

Self-administration is an experimental method that tests whether a drug has rewarding properties in animals. In this technique, animals are trained to press a lever a specific number of times in order to receive a known drug of abuse. Once responding is stable, a test drug with unknown properties is substituted for the training drug to determine if the test drug will maintain lever pressing. If the test drug has rewarding properties, animals will continue to lever press for the test drug at a rate that is greater than that of placebo.

In monkeys trained to self-administer the NMDA antagonist PCP (Schedule II), DXM maintained self-administration in 5 of 6 animals (Nicholson et al., 1999) at doses ranging from 100-300 µg/kg/infusion (i.v.). However, lower and higher doses of DXM that were tested (30 and 1000 µg/kg/infusion, i.v.) did not produce self-administration. These data are consistent with those from a rat study in which animals failed to self-administer a 1000 µg/kg/infusion (i.v.) dose of DXM (Jun et al., 2004).

The ability of DXM to produce self-administration is similar to that of other NMDA antagonists, including PCP (Schedule II) (Winger et al., 2002; Winger et al., 1989; Weissman et al., 1989; Marquis et al., 1989; Koek et al., 1988) and ketamine (Schedule III) (Winger et al., 2002; Winger et al., 1989; Koek et al., 1988).

Drug Discrimination Studies

Drug discrimination is an experimental method in which animals identify whether a test drug produces physical or behavioral effects similar to those produced by another drug with known pharmacological properties. For abuse assessment purposes, an animal is first trained to press one bar when it receives a known drug of abuse (the training drug) and another bar when it receives 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 more like the known drug of abuse or more like placebo. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing $\geq$80% on the bar associated with the training drug.

A limited number of drug discrimination studies have been conducted with DXM. The design of these studies has been based on the binding profile of DXM as an NMDA antagonist and a sigma-1 receptor agonist.

In rats trained to discriminate the NMDA antagonist, PCP (Schedule II), from saline, DXM produced dose-dependent generalization to the PCP cue (Nicholson et al., 1999). Similarly, in monkeys trained to discriminate PCP (Schedule II) from saline, DXM produced full generalization in 2 of 3 monkeys to the PCP cue, with the third monkey showing partial generalization (Nicholson et al., 1999). When pigeons were trained to discriminate PCP (Schedule II) from saline, DXM also produced full generalization to the PCP cue (Herling et al., 1983).

Similarly, when another NMDA antagonist, ketamine (Schedule III), was used as the training drug in a discrimination study in rats, DXM dose-dependently produced full generalization to the ketamine cue, as did PCP (Schedule II) (Narita et al., 2001).

A symmetrical generalization exists between DXM and NMDA antagonists in drug discrimination studies. Thus, when the discrimination training is reversed so that rats were trained to discriminate DXM from saline, the NMDA antagonists dizocilpine and dextrorphan produced full generalization to the DXM cue (Gavend et al., 1995).

DXM has also been tested for its ability to generalize to sigma-1 receptor agonists. When monkeys were trained to discriminate (+)pentazocine (Schedule IV), a high affinity agonist at sigma-1 receptors (Largent et al., 1987) from saline, DXM produced full generalization to the (+)pentazocine cue (White and Holtzman, 1982). Similarly, in monkeys trained to discriminate cyclazocine (unscheduled), another high affinity agonist at sigma-1 receptors (Largent et al., 1987) from saline, DXM produced full generalization to the cyclazocine cue (Holtzman, 1980). Symmetrical generalization also exists between DXM and sigma-1 receptor agonists, such that when animals were trained to discriminate

DXM from saline, the sigma-1 receptor agonist, cyclazocine (unscheduled), produced full generalization to the DXM cue (Gavend et al., 1995).

Human Pharmacokinetics of Dextromethorphan

In humans, DXM is well absorbed from the gastrointestinal tract with a Tmax of ~1.7 to 2.5 hours (Meyyanathan et al., 2008). Onset of effect is rapid, often beginning ~15 to 30 minutes after oral ingestion (Pender & Parks, 1991). The half-life of DXM is ~2.5 hours (Meyyanathan et al., 2008)

Dextromethorphan converts to its major metabolite, dextrorphan (DXO), through O-demethylation, catalyzed by the cytochrome P-450 isozyme 2D6 (CYP2D6) (Schmider et al., 1997). This metabolism occurs after the first-pass effect following oral administration (Wu et al., 1995). Dextrorphan, like its parent compound, has high affinity for the NMDA channel site (Murray and Leid., 1984).

Human Abuse Related Study of Dextromethorphan

Human Abuse Potential Studies with Dextromethorphan

There are 5 published studies in the scientific and medical literature in which DXM was administered to humans to evaluate abuse-related effects. Three of these studies were designed to assess whether DXM produced opioid-like effects in non-tolerant, non-dependent opioid abusers. One of these studies evaluated the alcohol-like effects of DXM in detoxified alcoholics and in healthy volunteers. There is one prospective human abuse potential study conducted with DXM to assess abuse-related positive and negative subjective effects in healthy volunteers.

In a 1953 study conducted by Isbell and Fraser with non-tolerant, non-dependent former morphine abusers, acute doses of DXM (ranging from 10 to 100 mg, p.o. and s.c.) did not produce morphine-like subjective responses. In contrast, the structurally-related drugs levorphanol, levomethorphan and racemethorphan produced morphine-like effects. Subjects reported that 60 to 75 mg doses of DXM (p.o. and s.c.) produced adverse events such as dizziness, double vision, headache, nausea and vomiting. A 75 mg dose of DXM (p.o. and s.c.) did not produce significant changes in temperature, pulse rate or blood pressure. Respiratory rate was not altered by DXM, but respiration was decreased by the opioids, levorphanol and levomethorphan.

In 1971, Jasinski et al. conducted a study in which DXM was administered to non-dependent opioid-experienced subjects at doses of 120 and 240 mg (p.o.) and 60, 120 and 240 mg (s.c.). In these individuals, DXM produced no opioid-like responses (such as increases in “Drug Liking”, “Euphoria” or identification of the drug as an opioid). However, DXM did produce increased responses on “Drunken”, “Sedation”, “Sleepy”,

"Nervous" and "Dysphoria" measures. Both subjects and observers identified DXM as a barbiturate (substances that are variably controlled under the CSA in Schedules II to IV).

In 2000, Jasinski et al. conducted a study in which DXM (180 mg, p.o.) was administered to "opiate abusers" (no further information about this subject population was provided). DXM did not increase ratings on the ARCI-MBG[1] "Euphoria" scale, Visual Analog Scale (VAS) "Feel Drug" or VAS "Drug Liking". However, this dose of DXM did increase ratings on VAS "Dislike Drug".

In 2000, Soyka et al. conducted a study in which DXM (140 mg, p.o.) was administered to detoxified alcoholics and to healthy volunteers. In both subject populations, DXM increased ratings on the Alcohol Sensations Scale. Alcoholic subjects also had an increase in VAS "Craving for Alcohol" scores following DXM administration.

In 2010, Zawertailo et al. conducted a study in which DXM (140, 210, 315 mg, p.o.) was administered to healthy volunteers who were not dependent on any drugs but who had a history of recreational drug use. In this population, DXM dose-dependently increased ratings on positive subjective scales (ARCI-MBG) "Euphoria" scale, VAS "Drug Liking", VAS "Good Effect", VAS "High") as well as negative subjective scales (VAS "Bad Effect", VAS-"Dizziness", ARCI-PCAG[2] "Sedation" scale, ARCI-(LSD[3] "Dysphoria" scale, ARCI "Unpleasantness" scale). DXM also dose-dependently induced a decrement in performance on two psychomotor tests: the Manual Tracking Test and the Digit Symbol Substitution Test.

Human Effects of Dextrorphan

Two clinical studies have sought to evaluate whether the DXM metabolite, DXO, is responsible for the psychoactive effects of DXM in humans (Zawertailo et al., 1998 and 2010), using poor and extensive CYP2D6 metabolizers, and administration of quinidine to inhibit CYP2D6 activity. In these studies, DXM was administered in doses ranging from 90 to 315 mg (p.o.). These small studies (n = 6-8) suggest that both DXM and DXO contribute positive and negative subjective responses to the overall experience following DXM ingestion.

Human Deaths and Overdoses with Dextromethorphan Reported in Medical Literature

In 2005, five teenage males in [redacted] (b) (6) died following ingestion of DXM, with or without other drugs. In each case, the deaths were deemed to be the result of direct toxic effects of DXM (Logan et al., 2009). These five deaths led to the publication of an FDA Talk Paper on DXM ("*FDA Warns Against Abuse of*

[1] Addiction Research Center Inventory-Morphine Benzedrine Group subscale is a measure of euphoria.

[2] Addiction Research Center Inventory-Pentobarbital-Chlorpromazine-Alcohol Group subscale is a measure of sedation.

[3] Addiction Research Center Inventory-Lysergic Acid Diethylamide Group subscale is a measure of hallucinations or dysphoria.

Dextromethorphan", May 20, 2005) to warn the public about the risks associated with abuse of DXM.

These five deaths following DXM use are described below:

- Two males (17 and 19 years old) in (b) (6) who had ingested DXM were found dead. Autopsy found pulmonary edema, cerebral edema and the presence of frothy foam in oropharynx and major airways in both individuals. The cause of death in both cases was determined to be acute DXM intoxication. Toxicology showed a heart blood DXM concentration of 3230 µg/L in the 17 year old and 1890 µg/L in the 19 year old, who also showed diphenhydramine levels of 20 µg/L. Both individuals tested positive for the presence of cannabinoids (levels not given).

  A clear plastic bag with 47 grams of a white powder was found in their possession with a label that said, "dextromethorphan Hbr 100 g, not for human use." The youths had previously consumed OTC cold medication that contained DXM, prior to use of the bulk powder formulation. According to a law enforcement investigation, the youth had obtained the DXM from "Chemical API," a chemical resale company in Indianapolis that purchased powdered DXM from India, repackaged the substance and resold it over the Internet. The youth had obtained the powdered DXM and repackaged it into gelatin capsules, which they intended to sell.

- A 19 year old male in (b) (6), who had ingested DXM was found unresponsive at his home on the floor. An hour later, he was pronounced dead, with the only finding upon autopsy being pulmonary edema. Toxicology showed DXM levels of 1300 µg/L in iliac blood. The cause of death was deemed to be DXM toxicity. It was determined that the young man had obtained the DXM from "Chemical API."

- Two 19 year old males in (b) (6), who had ingested powdered DXM (from "Chemical API"), Robitussin HL (containing DXM) and OTC Benadryl (diphenhydramine) were found dead. Autopsy reports showed that both individuals had heavy, wet, congested lungs. Toxicology showed iliac blood DXM concentrations of 950 and 3080 µg/L and diphenhydramine concentrations of 264 and 238 µg/L. The cause of death was deemed to be DXM toxicity.

Overdoses related to these cases were also reported:

- In the (b) (6) case, there were at least three cases of non-fatal overdose, two of which resulted in emergency department treatment. Each of these was cases was linked to the sale of the capsules containing powdered DXM that had been repackaged by one of the youth who died.

- In the case from (b) (6), one male youth also ingested the same amounts of powdered and OTC DXM in addition to diphenhydramine that killed his friends. Following the drug ingestion, he subsequently became ill and vomited. It is thought that he survived the drug ingestion because of vomiting and because he weighed ~70 pounds more than the friends who died.

In addition to the deaths in the U.S., the first published reports of death with DXM involved two young people in Sweden who died following a DXM overdose, including one deliberate suicide (Rammer et al., 1988).

Published Reports of Subjective Responses to Dextromethorphan

In a review paper, Boyer (2004) describes four plateaux of subjective response to DXM ingestion. In the first plateau (1.5 to 2.5 mg/kg; 105-175 mg), individuals describe mild intoxication that is similar to that of marijuana , accompanied by gastrointestinal symptoms. In the second plateau (2.5 to 7.5 mg/kg; 175-525 mg), responses include lethargy, agitation, ataxia, nystagmus and tachycardia. As the dose increases and individuals reach the third plateau (7.5 to 15 mg/kg; 525-1050 mg), frank psychotic symptoms, disorientation and seriously altered judgment often occur, similar to that of hallucinogens (Schedule I). Finally, at the fourth plateau (greater than 15 to 30 mg/kg; 1050-2100 mg), individuals experience fully dissociative states and hyperthermia, with the risk of seizures and aspiration.

Effects at doses greater than 120 mg include out-of-body experiences, dreamy state, disorientation, depersonalization, confusion, somnolence/stupor, impaired coordination, agitation, distorted movement and speech, dissociative anesthesia, visual hallucinations, altered mental state, ataxia, and nystagmus (Shin et al., 2008). At supratherapeutic doses (> 2 mg/kg, ~140 mg), DXM produces dissociative effects, tachycardia, hypertension, and respiratory depression (Romanelli and Smith, 2009).

Adverse Events Associated with Dextromethorphan

The medical and scientific literature has reported on adverse events (AEs) resulting from acute ingestion of DXM for over 50 years. These AEs include such symptoms as mood changes, perceptual alterations, inattention, disorientation and aggressive behavior, nausea, restlessness, insomnia, ataxia, slurred speech, and nystagmus (Isbell and Fraser 1953; Katona and Wason 1986; Rammer et al 1988; Hildebrand et al 1989).

Based on a review of medical case reports published through 2008, Romanelli and Smith (2009) identified that supratherapeutic doses (> 2 mg/kg, ~140 mg) of DXM produce tachycardia, hypertension, and respiratory depression. Severe folate deficiencies have also been reported in DXM abusers (n = 57) compared to users of other psychoactive substances (n = 47) (Au et al., 2007).

Bromism from Chronic Dextromethorphan Use

Because dextromethorphan is commonly available in hydrobromide form, bromism is possible in chronic users, characterized by memory impairment, drowsiness, tremors and ataxia, frequent skin eruptions, and psychiatric symptoms such as delirium or psychosis (Ng et al., 1992). However, bromism appears to be a rare condition that requires serum bromide levels greater than 50-100 mg/dl (Wolfe and Caravati, 1995).

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DSaRM Advisory Committee Background Information

The Role of Dextromethorphan in Treatment of Cough: A Clinical Perspective

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Role of Dextromethorphan in Treatment of Cough
A Clinical Perspective

Dextromethorphan was developed in the 1950's as part of a research project assigned with the task of finding a "nonaddictive substitute for codeine." It has been available as an over-the-counter cough suppressant since 1958 and dextromethorphan is included in the original monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use Proposed Rule in 1976 as an antitussive medication.[1] The Proposed Rule classified antitussives according to principal site of action and dextromethorphan was classified as a non-narcotic centrally acting antitussive medication. The Final Rule, issued in 1987, changed the classification of antitussives to oral and topical. Dextromethorphan was included as an active ingredient for oral medications, along with codeine and chlophedianol.[2] Due to its' addiction and abuse potential, codeine is not available over-the-counter in most locations. Chlophedianol is not marketed in the United States which leaves dextromethorphan as the only oral over-the-counter antitussive medication available in most states.

The 1987 Final Rule approves dextromethorphan for the following indications:[3]

1. Temporarily "*alleviates, calms, controls, decreases, quiets, reduces, relieves,* or *suppresses*" cough due to "*minor bronchial irritation* or *minor throat and bronchial irritation*" "*as may occur with, associated with,* or *occurring with*" "*a cold* or *the common cold*" or inhaled irritants.
2. Temporarily "*alleviates, calms, controls, decreases, quiets, reduces, relieves,* or *suppresses*" cough "*as may occur with, associated with,* or *occurring with*" "*a cold* or *the common cold*" or inhaled irritants.
3. The label may contain any one or more of the following statements:
    a. Cough suppressant which temporarily "*alleviates, controls, decreases, reduces, relieves,* or *suppresses*" the impulse to cough
    b. Temporarily helps you cough less
    c. Temporarily helps to "*alleviate, control, decrease, reduce, relieve,* or *suppress*" the cough reflex that causes coughing
    d. Temporarily "*alleviates, controls, decreases, reduces, relieves,* or *suppresses*" the intensity of coughing
    e. "*Alleviates, controls, decreases, reduces, relieves,* or *suppresses*" "*cough, the impulse to cough,* or *your cough*" to help you "*get to sleep, sleep,* or *rest.*"
    f. For products containing chlophedianol, dextromethorphan, or codeine: Calms the cough control center and relieves coughing.
    g. For products containing chlophedianol, dextromethorphan, camphor, or menthol: Non-narcotic cough suppressant for the temporary "*alleviation, control, decrease, reduction, relief,* or *suppression*" of cough.

The Proposed Rule included 23 references reviewed by the FDA Panel related to oral antitussives. The studies discussed in these references were done many years ago and many do not meet current regulatory standards; however, they were the available data at the time the monograph was being developed. A summary of selected references is included below:

- Benson, et al[4] compared several products, including dextromethorphan, for antitussive activity and analgesic activity. Antitussive activity was observed in unanesthetized dogs in which cough were induced by submucosal electrical stimulation of the trachea. The antitussive activity was compared to that of codeine and morphine. Codeine (dosed at 2.0 mg/kg) produced a maximum of 76% reduction in the number of coughs. Morphine at a similar dose produced a maximum of 45% reduction. Dextromethorphan, in a dosage of 2 mg/kg, inhibited the number of coughs a maximum of 62%; an 8 mg/kg dose produced an 88% reduction. Additionally dextromethorphan suppressed coughs without inducing ataxia, lethargy, and sleep.

- Stefko, et al,[5] evaluated antitussive drugs in cats and dogs. Cats were anesthetized and cough attacks were provoked by exposure to ammonia. Dogs were unanesthetized and cough was induced by electrical stimulation or dogs with upper respiratory infections (URI) were evaluated. In the electrically stimulated dogs, dextromethorphan dosed at 2 mg/kg inhibited cough by an average of 63% at 30 minutes and 68% at 60 minutes. This was similar to the results for codeine dosed at 2 mg/kg with 78% inhibition at 30 minutes and 76% at 60 minutes. Hydrocodone was the most effective with 100% cough inhibition at 30 and 60 minutes when dosed at 2 mg/kg, however, the dogs were markedly sedated. In the dog with URI dosed at 4 mg/kg, the cough ceased in 15 minutes and the duration of relief was 65 minutes. The dog with URI treated with hydrocodone at 1 mg/kg had cessation of the cough in 15 minutes with a duration of action of 80 minutes but the dog was very lethargic. The authors concluded dextromethorphan has a cough suppressant effect that is fairly rapid in onset and comparable in potency to codeine. Hydrocodone has greater antitussive activity but more side effects.

- Bickerman, et al,[6] evaluated the response to antitussive drugs after exposure of healthy humans to citric acid vapor. The placebo medications showed no significant cough suppression. At a dose of 10mg, dextromethorphan reduced coughs by 26.3% over four hours. In comparison, a 30 mg dose of codeine reduced cough by 22.4% over four hours.

- Cass, et al,[7] tested three strengths of dextromethorphan (6, 12, and 18 mg), codeine 15mg, and placebo in patients with persistent cough. Each treatment was given for seven days and cough suppression was recorded three times daily using a numerical scale. A good dose-response relationship was noted with dextromethorphan and all treatments were significantly more effective than placebo. The authors concluded that codeine 15 mg and a dose of dextromethorphan between 12 and 18 mg are equi-active but the incidence of untoward reactions was higher after using codeine.

- Nathan Ralph[8] described a study of dextromethorphan in 183 patients; 156 symptomatic with cough and 27 with no cough symptoms. It should be noted that 119 patients had tuberculosis. Cough severity was graded using a numerical scale. Initially dextromethorphan was dosed at 4 mg q.i.d. but after discussion with Cass and Frederik (see above) the dose was increased to 15 mg q.i.d. for 91 patients and 75

mg daily for seven patients. In the 144 patient evaluated for antitussive effectiveness, 15.9% had minimal or no relief, 46.5% had moderate relief, and 37.5% had marked or complete relief of cough. The 15 mg q.i.d. dosing was more effective than 4 mg doses. There were 12 patients with cough and 27 patients without cough who were given dextromethorphan to detect adverse events. Twenty-three patients were given 75 mg daily for several weeks with no significant ill effects. The author concludes dextromethorphan is a safe and effective cough-suppressing agent with antitussive activity similar to codeine but without the addictive properties or side effects typical of codeine.

Cough is one of the most common symptoms for which patients seek medical attention. Statistics from CDC[9] show acute upper respiratory infection was the leading illness-related diagnosis at emergency department visits in 2003 and the leading patient complaints that year were abdominal pain, chest pain, fever, and cough. For many conditions, cough may be the initial or even the only symptom.

The medical evaluation focuses on the duration of the cough and the most likely causes. Treatment of cough may vary, depending of the etiology. To further confuse things, patients may have cough caused by more than one disease and the diseases may have different treatments. The initial step in evaluation of cough is determining the duration of the cough. Based on the duration, cough is divided into three classifications. (These classifications are needed to fully understand the clinical guidelines that have been developed for treatment of cough.)

1. Acute: < 3 weeks duration
2. Subacute: 3 – 8 weeks duration
3. Chronic: > 8 weeks duration

The search for current clinical guidelines for treatment of cough involved reviewing the recommendations from several professional organizations including: American College of Physicians, American Lung Association, American College of Family Medicine, and American College of Chest Physicians. The American College of Chest Physicians (ACCP) is a professional organization focusing of respiratory disease and their guidelines for evaluation and treatment of cough are considered the standard that most other organizations follow. The ACCP originally published an evidence-based consensus panel report of cough in 1998 and a comprehensive update was published in 2006.[10] The consensus panel for the 2006 guidelines had extensive worldwide representation and recommendations for treatment of cough were made based on cough duration and likely etiology.

References to support the guidelines are from published literature; it should be noted these studies have not been formally reviewed by FDA. The recommendations were graded by the panel based on the quality of the evidence; the panel looked at available studies, the study designs, and the strength of the methodologies. The grading scale for the recommendations is:

A – Strong
B – Moderate

C – Weak
D – Negative
I – Inconclusive
E – Expert Opinion Only

The ACCP guidelines are extensive are provide recommendations based on the specific etiology of the cough. Recommendations related to dextromethorphan (as an oral antitussive agent) are included in several conditions which are listed below:

1. *Chronic Cough due to Acute Bronchitis:* In patients with a diagnosis of acute bronchitis, antitussive agents (dextromethorphan, codeine) are occasionally useful and can be offered for short-term symptomatic relief of coughing.
   Grade of Recommendation: C (weak)
2. *Chronic Cough due to Chronic Bronchitis:* In patients with chronic bronchitis, central cough suppressants such as codeine and dextromethorphan are recommended for short-term symptomatic relied of coughing.
   Grade of Recommendation: B (moderate)
3. *Post Infectious Cough not due to bacterial sinusitis or early Bordetella pertussis infection:* Central acting antitussive agents such as codeine and dextromethorphan should be considered when other measures fail. (Other measures include inhaled ipratropium, inhaled steroids, or oral steroids.)
   Grade of Recommendation: E/B (moderate; based on expert opinion)
4. *Cough due to Upper Respiratory Infection:* In patients with cough due to URI, central cough suppressants (codeine, dextromethorphan) have limited efficacy for symptomatic relief and are not recommended.
   Grade of Recommendation: D (negative)
5. *Acute Cough due to the Common Cold:* In patients with acute cough due to the common cold, OTC combination cold medications (including dextromethorphan) are not recommended until randomized controlled trials prove they are effective cough suppressants. The exception is the combination of an older antihistamine with a decongestant; this combination may be helpful to reduce cough.
   Grade of Recommendation: D (negative)

There were numerous published studies used as reference for the guidelines. The references specifically involving an evaluation of dextromethorphan are summarized below:

- Croughan-Minihane,[11] et al, conducted a multipractice, office-based, randomized clinical trial comparing guaifenesin, guaifenesin plus codeine, or guaifenesin plus dextromethorphan in patients with uncomplicated upper respiratory tract infections. Patients were randomly assigned to treatment and efficacy was assessed by telephone interviews at 2, 4, and 10 days. There were 97 patients in the trial. At day 2, 57 patients (59%) were contacted and 84% were continuing their treatment. By day 4, 70 patients (72%) were contacted and 54% continued on treatment. On day 10, 67 patients (69%) were contacted and 19% were still on the medication. The only statistically significant difference among treatment groups was the patient's ability to keep up with usual activities at day 4; 50% of patient in the codeine group were "able to keep up" compared to 14% in the dextromethorphan group and 30% in the

guaifenesin alone group. All other measures assessed (cough improved, no absenteeism, no trouble getting to sleep, not awakening from sleep, and fewer bouts of coughing) showed no difference between the treatments. The authors concluded codeine, dextromethorphan, and guaifenesin were equally effective in relieving cough symptoms and had similar side-effect profiles.

- Parvez, et al,[12] conducted three randomized, double blind, placebo controlled clinical trials in patients with acute upper respiratory tract infections. Cough was assessed using a standardized computer system measuring cough counts, latency, and total effort. Patients also provided subjective 'grades' of global assessment of cough and the troublesomeness of their cough on a 1-100 scale. The studies were conducted at a pharmaceutical research center. A total of 451 patients were evaluated over three years. In all three studies, the single 30 mg dose of dextromethorphan produced a greater reduction of cough bouts than the placebo though the number decreased after both treatments. The differences between dextromethorphan and placebo ranged from 19% (study 1 and 3) to 36% (study 2) but there was statistical significance only at certain time points, not for the entire treatment period and both treatments showed a decrease in cough bouts. The global cough assessment tended toward improvement with dextromethorphan; the score improved from 47 ± 25.8 pretreatment to 25.7 ± 22.5 at 120 minutes compared to the placebo pretreatment score of 47.6 ± 25 decreasing to 30.7 ± 25 but this was not statistically significant.

- Lee, et al,[13] evaluated objective and subjective measurements of cough in a double blind, randomized and parallel group design study comparing a single 30 mg dose of dextromethorphan and placebo in patients with cough due to acute upper respiratory tract infection. Cough frequency was recorded and cough sound pressure was measured using a microphone at the patient's throat. Patients also completed a subjective questionnaire to determine cough severity. A total of 43 patients were included; patients were evaluated for 180 minutes after medication administration. Both groups showed a decrease in cough frequency; for patients treated with dextromethorphan the median frequency decreased from 50 to 19 and for those receiving placebo it decreased from 42 to 20.5. Though the dextromethorphan decrease was larger, it was not statistically significant. The subjective cough severity scores decreased in both groups and the difference was not significant. The authors conclude this study provides little support for the antitussive activity of a single 30 mg dose of dextromethorphan in patients with cough associated with acute URI.

- Pavesi, et al,[14] conducted a meta-analysis to evaluate the antitussive effect of treatment with dextromethorphan 30 mg vs. placebo over a 3 hour period in patients with cough due to uncomplicated URI. The six studies used for the meta-analysis were randomized, double blind, parallel group, single-dose, placebo controlled studies evaluating cough for three hours after dosing. The studies were financed by a pharmaceutical company. The meta-analysis was based on a total of 710 subjects. The individual studies were not powered to show statistical significance. The analysis showed significant treatment differences between placebo and dextromethorphan 30 mg for total cough bouts, total cough components, cough effort, and cough latency,

but not for cough intensity. The largest reduction in cough bouts and components and improvement in latency occurred between 90 and 120 minutes after dextromethorphan dosing. The average treatment difference was 12 to 17%. The authors believe this work demonstrates the small but measurable benefit of dextromethorphan over placebo for this condition.

- Schroeder and Fahey[15] conducted a systematic review of randomized controlled trials for treatment of acute cough in the ambulatory setting. A total of 15 trials were reviewed. Two trials tested dextromethorphan versus placebo; one study favored dextromethorphan (the Parvez trial) and the other showed no significant effect (the Lee trial). The authors concluded it remains unclear whether OTC cough preparations are helpful in acute cough and the advice to use them should be restricted until more evidence becomes available on their effectiveness.

In addition to these references, Smith, et al,[16] published a second update to the Cochrane Review originally conducted in 2001 and updated in 2004. This review evaluated 25 trials, three which included dextromethorphan (Parvez, Lee, and Pavesi). The authors noted no good evidence for or against the effectiveness of OTC medications in acute cough. They also note that many studies were of low quality and had very different designs making evaluation of overall efficacy difficult.

In summary, cough is a very common symptom and results in many medical visits yearly. Cough has many possible etiologies and may have more than one etiology in the same patient. Appropriate treatment of cough is largely determined by the etiology and/or the duration of the cough. There are a few situations where dextromethorphan is clearly beneficial for treatment of cough though we know the drug is commonly used. The options for nonprescription cough therapy are limited and there are no other oral OTC antitussive agents widely available in the United States.

References

Included in the background material are references 4, 5, and 6 as examples of studies used to support the monograph. Also included are reference 10, the Executive Summary of the ACCP Guidelines, and the 2009 Cochrane review (reference 15) as the most significant current references. The Cochrane review includes summaries of the studies presented in references 11, 12, and 13.

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[1] 41FR38312
[2] 52FR30042
[3] 52FR30055
[4] Benson WM, Stefko PL, and Randall LO, "Comparative Pharmacology of Levorphan, Racemorphan and Dextrorphan and Related Methyl Ethers," *Journal of Pharmacology and Experimental Therapeutics,* 109:189-200, 1953.
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 13, 2010
To:	Michael Klein, MD Supervisory Pharmacologist Controlled Substance Staff Office of the Center Director
Thru:	Laura A. Governale, Pharm.D., MBA Drug Utilization Data Analysis Team Leader Division of Epidemiology Office of Surveillance and Epidemiology
From:	Tracy Pham, Pharm.D Drug Use Data Analysts Division of Epidemiology Office of Surveillance and Epidemiology
Subject:	Over-the-Counter (OTC) and Prescription Dextromethorphan Utilization, Years 2000 to 2009
Drug Name(s):	Single-ingredient and combination dextromethorphan products
Application Type/Number:	Multiple
Applicant/sponsor:	Multiple
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CONTENTS

EXECUTIVE SUMMARY

This review provides drug utilization patterns for over-the-counter (OTC) sales and outpatient dispensed prescriptions for single-ingredient and combination dextromethorphan containing products in the U.S. from year 2000 to year 2009. Proprietary drug use databases licensed by the FDA were used to conduct this analysis. Data findings are as followed:

- Sales of OTC and prescription dextromethorphan products distributed as bottles from manufacturers to retail and non-retail channels of distribution increased by approximately 19% from year 2005 to year 2009. OTC dextromethorphan products had a higher proportion of sales than prescription dextromethorphan products. Over the years, sales of OTC dextromethorphan products increased by approximately 22% whereas sales for prescription dextromethorphan products decreased by approximately 22%. Moreover, sales of OTC single-ingredient and combination dextromethorphan products increased by approximately 11% and 23%, respectively.
- The majority of OTC dextromethorphan products (92-93%) were sold as combination products during the study period. Acetaminophen was commonly found in OTC combination dextromethorphan products, followed by phenylephrine and guaifenesin in year 2009.
- Oral liquid formulations (60-64%) accounted for the majority of sales of OTC combination dextromethorphan products from year 2005 to year 2009, followed by regular oral solid formulations, long-acting oral solid formulations and mouth/throat topical formulations. Non-specific oral liquid, syrup and read-made oral suspension formulations accounted for the highest proportion of sales of oral liquid formulations.
- Oral liquid formulations (80-86%) of OTC single-ingredient dextromethorphan products again were sold more than regular oral solid formulations and mouth/throat topical formulations.
- From year 2000 to year 2009, nearly 100% of prescription dextromethorphan products were dispensed as combination products. Phenylephrine and chlorpheniramine followed by pseudoephedrine and carbinoxamine were the most common ingredients found in prescription dextromethorphan combination products in year 2009.
- Codeine containing products accounted for the highest proportion of dispensed prescriptions among the cough/cold products, followed by benzonatate, hydrocodone containing products and dextromethorphan containing products. While the number of dispensed prescriptions for codeine containing products and benzonatate increased from year 2000 to year 2009, the number of prescriptions dispensed for hydrocodone containing products and dextromethorphan containing products decreased.
- Codeine containing products, benzonatate, hydrocodone containing products and dextromethorphan containing products were most commonly prescribed by general practice/family medicine/osteopathic specialists and internal medicine specialists during the examined time period.
- In year 2009, the majority of dispensed prescriptions for dextromethorphan containing products were for patients aged 0 to 10 years old while the majority of dispensed prescriptions for codeine containing products, benzonatate and hydrocodone containing products were for patients aged 51 to 60 years old.

1 INTRODUCTION

In preparation for the Drug Safety and Risk Management Advisory Committee meeting on dextromethorphan abuse on September 14, 2010, the Division of Epidemiology was requested by the Controlled Substances Staff (CSS) to provide an analysis of the OTC and outpatient prescription utilization patterns for single-ingredient and combination dextromethorphan containing products in the U.S. for years 2000 to 2009.

2 BACKGROUND

Dextromethorphan is a cough suppressant agent which is often used in combination with various active ingredients in many cough/cold OTC and prescription products. When consumed at high doses exceeding the maximum recommended dosages on the label, dextromethorphan causes euphoria, hallucination, distorted visual perceptions, loss of motor coordination, dissociative sedation, psychosis and even death.[1]

In response to the number of reported cases of deaths and increases in abuse associated with dextromethorphan use among teenagers, the Controlled Substance Staff requested an analysis of the OTC and prescription utilization of dextromethorphan to put these reports into context. A Drug Safety and Risk Management Advisory Committee meeting is scheduled for September 14, 2010, to assess the abuse liability of dextromethorphan and to determine whether or not to mandate dextromethorphan as a scheduled substance. In support of these assessments, this review summarizes the sale of OTC single-ingredient and combination dextromethorphan products for year 2005 to year 2009. The outpatient utilization for prescription single-ingredient and combination dextromethorphan products was also analyzed for year 2000 to year 2009.

3 METHODS AND MATERIAL

3.1 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis (see Appendix 2 for full database descriptions).

The IMS Health, IMS National Sales Perspective™ was used to analyze the total sales of OTC single-ingredient and combination dextromethorphan products as measured in eaches (packages, bottles, etc.), or bottles, sold from manufacturers to retail and non-retail channels of distribution for year 2005 to year 2009. OTC dextromethorphan sales were also analyzed by formulation and active ingredient for combination products.

The SDI, Vector One®: National (VONA) was used to obtain estimates of the number of outpatient prescriptions dispensed for dextromethorphan products for year 2000 to year 2009. Estimates of the number of outpatient dispensed prescriptions for dextromethorphan products and its comparators were stratified by class and prescribing specialties for year 2000 to year 2009. Since SDI, VONA data stratified by age are only available from year 2002 and forward, estimates of the number of outpatient dispensed prescriptions for dextromethorphan products and its comparators were stratified by patient age from year 2002 to year 2009. Dextromethorphan's comparators include benzonatate, and non-analgesic codeine- and hydrocodone-containing products.

4 RESULTS

4.1 OVERALL DEXTROMETHORPHAN USE (TABLE 1, FIGURES 1-2)

During the study period from year 2005 to year 2009, the sale of OTC and prescription dextromethorphan products, as a whole, distributed directly from manufacturers to retail and non-retail channels of distribution in the U.S. increased by approximately 19% from 145 million bottles to 173 million bottles (Table 1, Figure 1). OTC dextromethorphan products accounted for the highest amount of sales (95-97%) over prescription dextromethorphan products. In year 2005, approximately 137 million bottles of OTC and 7.7 million bottles of prescription dextromethorphan products were sold, respectively. By year 2009, the sale of OTC dextromethorphan products increased by approximately 22% to 167 million bottles while the sale of prescription dextromethorphan products declined by approximately 22% to 6 million bottles.

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[1] Online Wikipedia: The Free Encyclopedia. Data collected in July 2010. Available at: http://en.wikipedia.org/wiki/Dextromethorphan

Combination OTC dextromethorphan products accounted for around 92-93% of all OTC dextromethorphan product sales while prescription dextromethorphan products were 100% sold as combination products throughout the study period (Table 1, Figure 2). In year 2005, approximately 127 million bottles and 10.2 million bottles of OTC combination and single-ingredient dextromethorphan products were sold, respectively. These numbers of bottles in sales increased by approximately 23% to 156 million bottles of OTC combination dextromethorphan products, and by approximately 11% to 11.3 million bottles of OTC single-ingredient dextromethorphan products in year 2009.

4.2 SALES OF OVER-THE-COUNTER DEXTROMETHORPHAN PRODUCTS

4.2.1 Single-Ingredient OTC Dextromethorphan Products by Dosage Forms (Table 1, Figures 3)

OTC single-ingredient dextromethorphan products comprised of oral liquid, regular oral solid and mouth/throat topical formulations. During the study period from year 2005 to year 2009, oral liquid formulations had the highest proportion of sales of all OTC single-ingredient dextromethorphan products, accounting for approximately 79-86%. Their sales increased by approximately 14% from 8.5 million bottles (83% of all OTC sing-ingredient dextromethorphan sales) in year 2005 to 9.7 million bottles (85% of all OTC sing-ingredient dextromethorphan sales) in year 2009. Throughout the study period, non-specific liquid formulations[2] (72-76%) and syrup (23-28%) were most commonly sold among the oral liquid formulations. By year 2009, the number of sales for non-specific liquid formulations and syrup increased by approximately 11% and 26%, respectively. Sale for oral drop formulations of oral liquid formulation peaked in year 2007 with approximately 296,400 bottles, but dropped to no reported sale in year 2009.

Regular oral solid formulations accounted for approximately 8-13% of sales of OTC single-ingredient dextromethorphan products from year 2005 to year 2009. Their sales increased by approximately 65% from around 900,000 bottles in year 2005 to 1.5 million bottles in year 2009. Among regular oral solid formulations, regular capsule formulations had the highest proportion of sales at 93-100% throughout the study period compared to regular uncoated tablet and regular coated tablet formulations. While sales of regular capsule formulations increased over the years, sales of regular uncoated tablet formulations decreased in recent years. Regular coated tablet formulations had no reported sale.

Mouth/throat topical formulations had the smallest proportion of sales at 2-8% of OTC single-ingredient dextromethorphan products from year 2005 to 2009. Their sales decreased by approximately 76% from 800,000 bottles sold in year 2005 (8% of sales) to 191,000 bottles sold in year 2009 (2% of sales). Mouth/throat topical formulations are available as mouth/throat all others, spray, lozenge and pressurized aerosol formulations with mouth/throat all others formulations[3] accounting for the majority of sales.

4.2.2 Combination OTC Dextromethorphan Products by Dosage Forms (Table 1, Figure 4)

OTC combination dextromethorphan products consisted of oral liquid, oral solid regular, oral solid long-acting and mouth/throat topical formulations. From year 2005 to year 2009, oral liquid formulations accounted for roughly 57-64% of OTC combination dextromethorphan products. Their sales generally increased by approximately 17% from 80 million bottles in year 2005 to 93.7 million bottles in year 2009. Of these oral liquid formulations, non-specific liquid (41.9 million bottles), syrup (38 million bottles) and ready-made oral suspension (11.6 million bottles) formulations accounted for approximately 97.5% of oral liquid formulation sales in year 2009. Elixir, oral drops, oral jelly and expectorant liquid formulations made up the remaining 2.5% of oral liquid formulation sales. While the absolute number and proportions of products sold for non-specific liquids and ready-made oral suspensions increased since year 2005, the sales of syrups, elixirs, oral drops, oral jellies and expectorant liquids of oral liquid formulation dropped.

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[2] Non-specific liquid formulations include oral liquids and solutions that do not fit into the traditional categories.

[3] Mouth/Throat All Others include oral gels, oral pastes, oral strips, swabs and lollipops.

Regular oral solid formulations accounted for approximately 30-34% of OTC combination dextromethorphan products during the study period. Their sales generally increased by approximately 16% from 42.8 million bottles in year 2005 to 49.4 million bottles in year 2009. Regular coated tablet formulations had the highest proportion of sale of regular oral solid formulations in year 2009, accounting for around 25.1 million bottles (51%), followed by regular capsule formulations with around 15.1 million bottles (31%) and regular uncoated tablet formulations with approximately 7.3 million bottles (15%). Since year 2005, the sales of regular coated tablet formulation increased by 79% while the sales of regular capsule formulations decreased by 13%. Sales of regular uncoated tablet formulations remained steady. Regular oral lozenges had little to no reported sale.

Among OTC combination dextromethorphan products, approximately 3-6% of sales of OTC combination dextromethorphan products were for long-acting oral solid formulations throughout the study period. Their sales approximately doubled from around 3.8 million bottles in year 2005 to 9.1 million bottles in year 2009. Long-acting oral solid formulations consisted of long-acting uncoated tablet formulations.

From year 2005 to year 2009, sales of mouth/throat topical formulations increased from approximately 11,500 bottles in year 2005 to a peak of 1.6 million bottles in year 2007, but then declined to 660,000 bottles in year 2009. Their sales accounted for approximately 0.4% of sales of OTC combination dextromethorphan products in year 2009.

4.2.3 Combination OTC Dextromethorphan Products by Ingredient (Figure 5)

During the study period from year 2005 to year 2009, dextromethorphan was the most common ingredient found in OTC cough/cold/flu market.[4] In year 2005, OTC combination dextromethorphan products containing pseudoephedrine (80.3 million bottles, or 63% of OTC dextromethorphan combination products) accounted for the highest proportion of sale, followed by acetaminophen (67 million bottles, or 53% of OTC dextromethorphan combination products), guaifenesin (46.7 million bottles, or 37% of OTC dextromethorphan combination products), doxylamine (25 million bottles, or 20% of OTC dextromethorphan combination products), chlorpheniramine (24.2 million bottles, or 19% of OTC dextromethorphan combination products) and phenylephrine (6.7 million bottles or 5% of OTC dextromethorphan combination products). By year 2009, sales of OTC combination dextromethorphan products containing acetaminophen, phenylephrine, guaifenesin, doxylamine and chlorpheniramine all increased while sales of OTC combination dextromethorphan products containing pseudoephedrine decreased. Sales of OTC combination dextromethorphan products containing acetaminophen increased by approximately 42% to 95.1 million bottles (61% of OTC dextromethorphan combination products) and became the number one commonly found ingredient in year 2009. Similarly, sales of OTC combination dextromethorphan products containing phenylephrine increased by approximately 9 fold to 65.3 million bottles (42% of OTC dextromethorphan combination products) and became the second most commonly found ingredient. Moreover, sales of OTC combination dextromethorphan products containing guaifenesin increased by approximately 37% to 64 million bottles (41% of OTC dextromethorphan combination products), making guaifenesin the third running up ingredient. Sales of OTC combination dextromethorphan products containing doxylamine (23% of OTC dextromethorphan combination products) and chlorpheniramine (20% of OTC dextromethorphan combination products) increased by approximately 45% and 28%, respectively, while sales of OTC combination dextromethorphan products containing pseudoephedrine (16% of OTC dextromethorphan combination products) decreased by approximately 69% in year 2009.

4.3 PRESCRIPTION DEXTROMETHORPHAN PRODUCTS (FIGURES 6-7)

During the study period from year 2000 to year 2009, nearly 100% of prescription dextromethorphan products were dispensed as combination products. Prescription single-ingredient dextromethorphan products accounted for approximately less than 1% of dispensed dextromethorphan prescriptions. The use of prescription combination dextromethorphan products decreased from approximately 9.2 million prescriptions in year 2000 to

[4] IMS Health. IMS National Sales Perspective™. Years 2005-2009. Extracted July 2010. File: 1007cou1.dvr

6.4 million prescriptions in year 2007, but then increased to 7.9 million prescriptions in year 2009. Meanwhile, the use of prescription single-ingredient dextromethorphan products continued to decline from approximately 23,400 prescriptions in year 2000 to 4,700 prescriptions in year 2009.

In year 2000, the most common ingredients found in prescription combination dextromethorphan products were pseudoephedrine and carbinoxamine (5.3 million prescriptions, 57.5%); followed by pseudoephedrine and brompheniramine (1.1 million prescriptions, 12%); pseudoephedrine and chlorpheniramine (533,500 prescriptions, 6%); phenylephrine and pyrilamine (59,700 prescriptions, 0.6%). Prescription combination dextromethorphan products containing phenylephrine and chlorpheniramine had no reported use in year 2000. By year 2009, the number of outpatient dispensed prescriptions for combination dextromethorphan products containing phenylephrine and chlorpheniramine increased to approximately 3.8 million prescriptions (48.5% of dextromethorphan prescriptions), making these the most common ingredients found in prescription dextromethorphan products. Meanwhile, the number of outpatient dispensed prescriptions for combination dextromethorphan products containing pseudoephedrine decreased over this time period.

4.3.1 Outpatient Dispensed Prescriptions for Dextromethorphan Products Among Cough/Cold Products Class (Figure 8)

During the study period from year 2000 to year 2009, the number of dispensed prescriptions for cough/cold products as a whole peaked at approximately 25.6 million prescriptions in year 2001, but declined to 15.4 million prescriptions in year 2009. When comparing among prescription cough/cold products from year 2000 to year 2009, codeine containing products were most commonly dispensed on the market. In year 2000, approximately 4.8 million prescriptions (21%) of dispensed cough/cold products were for codeine containing products, followed by dextromethorphan containing products with 3.8 million prescriptions (16%), hydrocodone[5] containing products with 3.8 million prescriptions (16%), and benzonatate with 3.3 million prescriptions (14%). By year 2009, codeine containing products continued to be the top commonly dispensed products among the cough/cold products on the market. The number of prescriptions dispensed for codeine containing products increased by approximately 39% to 6.7 million prescriptions (43.5% of the market). Meanwhile, the number of dispensed prescriptions for benzonatate increased by approximately 40% to 4.7 million prescriptions (31% of the market) in year 2009. Unlike codeine containing products and benzonatate, the number of prescriptions dispensed for hydrocodone containing products peaked at 4.7 million prescriptions in year 2005, but declined to 2.8 million prescriptions (18% of the market) in year 2009. Moreover, the number of dispensed prescriptions for dextromethorphan containing products peaked at 4.3 million prescriptions in year 2001, but decreased to 893,000 prescriptions (6% of the market) in year 2009.

4.3.2 Outpatient Dispensed Prescriptions for Dextromethorphan Products Among Cough/Cold Products Class by Prescribing Specialties (Table 2, Figure 9)

In year 2009, general practice/family medicine/osteopathic specialists (6.2 million prescriptions, 40%) followed by internal medicine specialists (3.4 million prescriptions, 22%) prescribed the majority of dispensed prescriptions for cough/cold products. Other specialists in the top-ten list who commonly prescribed these cough/cold products include nurse practitioners (7%); physician assistants (6.5%); pediatricians (5%); and emergency medicine (5%).

The most common product prescribed by general practice/family medicine/osteopathic specialists, internal medicine specialists, nurse practitioners, physician assistants, pediatricians, emergency medicine specialists and cardiologists were codeine containing products (Table 2). Benzonatate was the most common product prescribed by pulmonary disease specialists, hospitalists and ear, nose and throat specialists. Among the pediatric specialty, dextromethorphan containing products were the second most prescribed products following codeine containing products. Hydrocodone containing products were the second most prescribed products by pulmonary disease specialists and ear, nose and throat specialists.

[5] Hydrocodone-containing products – only cough/cold products; analgesic products excluded.

4.3.3 Outpatient Dispensed Prescriptions for Dextromethorphan Products Among Cough/Cold Products Class by Age (Figures 10 and 11)

Dispensed prescriptions for cough/cold products were analyzed for year 2002 to year 2009 and stratified by patient age in the following age groups: 0-10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71 years and older, and unspecified. In year 2002, the majority of prescriptions dispensed for dextromethorphan containing products were for patients aged 0 to 10 years (19% of dextromethorphan prescriptions), followed by patients aged 41 to 50 years (15% of dextromethorphan prescriptions) and patients aged 51 to 60 years (15% of dextromethorphan prescriptions) (Figure 11). By year 2004, the number of dispensed prescriptions for dextromethorphan containing products for patients aged 0 to 10 years decreased sharply and accounted for about 7.5% of overall dextromethorphan dispensed prescriptions; the majority of prescriptions for dextromethorphan containing products were dispensed to patients aged 31 years and older in that year and accounted for about 78% of dextromethorphan dispensed prescriptions. In year 2009, the number of dispensed prescriptions for dextromethorphan containing products for patients aged 0 to 10 years old increased again; patient aged 0 to 10 years (28%) received the majority of dispensed prescriptions for dextromethorphan containing products followed by the age 11-20 year olds (14%), and the age 71 years and greater (14%). During the study period from year 2005 to year 2009, the trends for the number of dispensed prescriptions for dextromethorphan containing products for patients aged 11 years and older continued to decrease.

In year 2009, the highest proportion of prescriptions dispensed for codeine containing products, benzonatate and hydrocodone containing products were for patients aged 51 to 60 years old (Figure 10), followed by patients aged 41 to 50 years old for codeine and hydrocodone containing products; the second highest proportion of use for benzonatate products were among patients aged 71 years and greater.

5 DISCUSSION

Findings from this consult should be interpreted in the context of the known limitations of the databases used. The IMS Health, IMS National Sales Perspectives™ data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use. Furthermore, IMS estimates that approximately 50% of all U.S. over-the-counter sales activity is captured in this database.[6]

Taking these database limitations into account, our analysis indicated that the majority of patient exposures to dextromethorphan products were OTC combination dextromethorphan products containing mostly acetaminophen, phenylephrine and guaifenesin in oral liquid formulations in recent years.

The dispensed prescription data provided by SDI, Vector One®: National (VONA) database captures retail prescription activity with a reasonable amount of certainty based on the large sample size of pharmacies and data projection methodology. However, data on over-the-counter product use is not captured in this database. A reliable estimate of over-the-counter product usage is not possible given the limitations of the drug usage databases available at the Agency's disposal. Unlike prescription transactions which capture detailed information on the drug product being dispensed as well as patient demographic data and prescribing specialty data, transactions for over-the-counter products are not captured in the same method. Furthermore, the ease of accessibility for over-the-counter products compared to prescription products and the PRN (as needed) nature of use make estimating over-the-counter product usage difficult. For these reasons, the true extent of use for over-the-counter dextromethorphan products alone or in combination with other drug products is at best underestimated in this analysis.

6 CONCLUSIONS

[6] IMS Health, IMS National Sales Perspectives™ Retail and Non-Retail Sample Coverage of the Universe (09/15/06).

During the study period from year 2005 to year 2009, the sale of OTC and prescription dextromethorphan products directed from manufacturers to retail and non-retail channels of distribution increased by approximately 19%. The oral liquid formulations of OTC dextromethorphan products accounted for the majority of sales. The majority of OTC dextromethorphan products were sold as combination products in which acetaminophen was the most commonly found co-active ingredient.

Prescription dextromethorphan products were most commonly dispensed as combination products. Phenylephrine and chlorpheniramine were commonly found ingredients in prescription combination dextromethorphan products in year 2009. When comparing among cough/cold products in year 2009, dextromethorphan containing products were dispensed less than codeine containing products, hydrocodone containing products and benzonatate. The number of dispensed prescriptions for dextromethorphan containing products also decreased since year 2000. General practice/family medicine/osteopathic specialists were the number one group of prescribers who commonly prescribed dextromethorphan containing products. The majority of dispensed prescriptions for dextromethorphan containing products were for patients aged 0 to 10 years old in year 2009.

APPENDIX 1: FIGURES AND TABLES

Table 1. Sales of Over-the-Counter and Prescription Dextromethorphan Products by Dosage Forms, Years 2005-2009

	YEAR									
	2005		2006		2007		2008		2009	
	Eaches***	%	Eaches	%	Eaches	%	Eaches	%	Eaches	%
SELECTED MARKET	**145,093,900**	**100**	**148,605,100**	**100**	**157,040,400**	**100**	**153,869,000**	**100**	**173,077,600**	**100**
OVER-THE-COUNTER	137,267,600	94.6	141,727,500	95.4	150,667,100	95 9	148,357,600	96.4	167,044,500	96.5
COMBINATION	127,092,900	92.6	131,961,200	93.1	138,985,200	92 2	138,073,900	93.1	155,703,800	93.2
SYSTEMIC ORAL LIQUID	80,032,600	63	84,764,800	64.2	85,281,800	61.4	79,300,400	57.4	93,704,800	60.2
NON-SPECIFIC LIQUID	24,437,100	30.5	35,021,800	41.3	36,764,700	43.1	33,465,700	42.2	41,869,700	44.7
SYRUP	40,694,400	50.8	34,320,400	40.5	31,722,000	37.2	34,069,500	43	37,984,500	40.5
REDY-MDE SUSPENSION ORA	4,200,500	5.2	6,893,800	8.1	9,590,800	11.2	9,056,700	11.4	11,550,500	12.3
ELIXIR	5,165,400	6.5	3,310,400	3.9	2,127,000	2 5	1,693,900	2.1	1,496,700	1.6
ORAL DROPS	4,837,000	6	4,546,800	5.4	4,201,700	4.9	416,600	0.5	462,300	0.5
ORAL JELLY	697,800	0.9	671,700	0.8	875,700	1	598,000	0.8	341,200	0.4
EXPECTORANT LIQUID	400	0	--	0	--	0	--	0	--	0
SYSTEMIC ORAL SOLID REG	42,758,300	33.6	40,766,900	30.9	44,847,200	32 3	47,467,100	34.4	49,417,500	31.7
TABS COATED REGULAR	14,026,900	32.8	13,794,200	33.8	20,419,100	45 5	22,176,800	46.7	25,105,900	50.8
CAPS REGULAR	17,416,600	40.7	16,241,700	39.8	13,715,000	30.6	13,872,800	29.2	15,102,000	30.6
TABS UNCOATED REGULAR	7,270,000	17	7,378,700	18.1	7,025,100	15.7	8,358,800	17 6	7,267,100	14.7
OTHR ORAL SOLID REGULAR	4,044,700	9.5	3,352,300	8.2	3,688,000	8.2	3,058,600	6.4	1,942,400	3.9
LOZENGE REGULAR	100	0	--	0	--	0	--	0	--	0
SYSTEMIC ORAL SOLID L/A	3,780,900	3	4,257,200	3.2	6,171,000	4.4	8,220,500	6	9,056,600	5.8
TABS UNCOATED LG/ACT	3,780,900	100	4,257,200	100	6,171,000	100	8,220,500	100	9,056,600	100
SYSTEMIC ALL OTHERS	509,600	0.4	762,000	0.6	1,085,700	0 8	2,083,100	1 5	2,864,800	1.8
SYSTEMIC KITS	509,600	100	762,000	100	1,085,700	100	2,083,100	100	2,864,800	100
MOUTH/THROAT TOPICAL	11,500	0	1,410,300	1.1	1,599,500	1 2	1,002,800	0.7	660,100	0.4
MOUTH THROAT ALL OTHERS	--	0	1,402,800	99.5	1,589,700	99.4	999,400	99.7	658,300	99.7
MOUTH THROAT LOZENGES	9,500	82.6	--	0	--	0	800	0.1	1,600	0.2
MOUTH AND THROAT SPRAY	2,000	17.4	7,500	0.5	9,800	0 6	2,700	0.3	200	0
SINGLE-INGREDIENT	10,174,600	7.4	9,766,300	6.9	11,681,900	7.8	10,283,600	6 9	11,340,700	6.8
SYSTEMIC ORAL LIQUID	8,474,600	83.3	8,415,500	86.2	9,629,500	82.4	8,199,000	79.7	9,664,200	85.2
NON-SPECIFIC LIQUID	6,451,600	76.1	6,205,300	73.7	7,063,400	73.4	5,937,500	72.4	7,160,800	74.1
SYRUP	1,981,700	23.4	2,123,000	25.2	2,269,700	23 6	2,261,200	27.6	2,503,400	25.9
ORAL DROPS	41,300	0.5	87,300	1	296,400	3.1	400	0	--	0
SYSTEMIC ORAL SOLID REG	900,400	8.8	976,100	10	1,301,700	11.1	1,425,600	13.9	1,485,600	13.1
CAPS REGULAR	900,300	100	911,900	93.4	1,234,600	94 8	1,391,900	97.6	1,485,500	100
TABS UNCOATED REGULAR	100	0	64,200	6.6	67,100	5 2	33,700	2.4	100	0
TABS COATED REGULAR	0	0	0	0	--	0	--	0	--	0
MOUTH/THROAT TOPICAL	799,600	7.9	374,700	3.8	750,700	6.4	659,000	6.4	190,900	1.7
MOUTH THROAT ALL OTHERS	3,300	0.4	3,600	1	534,800	71 2	467,600	71	110,500	57.9
MOUTH AND THROAT SPRAY	99,400	12.4	141,700	37.8	161,200	21 5	191,300	29	80,300	42.1
MOUTH THROAT LOZENGES	133,900	16.7	--	0	200	0	0	0	0	0
MTH THRT PRESUR AEROSOL	563,000	70.4	229,400	61.2	54,600	7 3	100	0	--	0
PRESCRIPTION	7,741,400	5.3	6,840,600	4.6	6,373,200	4.1	5,511,500	3.6	6,033,200	3.5
COMBINATION	7,741,400	100	6,840,500	100	6,373,200	100	5,511,500	100	6,033,200	100
SYSTEMIC ORAL LIQUID	6,676,400	86.2	5,973,400	87.3	5,678,000	89.1	5,408,200	98.1	5,942,300	98.5
SYRUP	3,704,900	55.5	3,103,800	52	2,896,600	51	3,094,000	57.2	3,823,500	64.3
ORAL DROPS	2,277,200	34.1	2,197,100	36.8	2,036,700	35 9	1,631,700	30.2	1,549,000	26.1
REDY-MDE SUSPENSION ORA	400,800	6	388,900	6.5	521,700	9.2	453,700	8.4	291,900	4.9
NON-SPECIFIC LIQUID	248,700	3.7	253,800	4.2	202,700	3.6	212,300	3 9	270,100	4.5
ELIXIR	43,200	0.6	28,700	0.5	20,300	0.4	16,500	0 3	7,800	0.1
EXPECTORANT LIQUID	1,600	0	1,000	0	0	0	0	0	--	0
SYSTEMIC ORAL SOLID REG	21,000	0.3	17,200	0.3	17,400	0.3	56,100	1	69,300	1.1
TABS UNCOATED REGULAR	20,200	96.2	16,000	92.9	16,200	93 2	44,700	79.6	56,300	81.1
CAPS REGULAR	--	0	0	0	--	0	11,400	20.4	13,100	18.9
TABS COATED REGULAR	800	3.8	1,200	7.1	1,200	6.8	0	0	--	0
SYSTEMIC ORAL SOLID L/A	1,043,900	13.5	849,900	12.4	677,900	10 6	47,100	0.9	21,500	0.4
TABS UNCOATED LG/ACT	934,300	89.5	765,700	90.1	623,700	92	44,600	94.7	21,400	99.5
TABS COATED LONG ACTING	88,500	8.5	84,200	9.9	54,100	8	2,500	5.3	100	0.5
CAPS LONG ACTING	21,100	2	100	0	0	0	--	0	--	0
SINGLE-INGREDIENT	--	0	0	0	0	0	--	0	--	0
SYSTEMIC ORAL LIQUID	--	0	0	100	0	100	--	0	--	0
REDY-MDE SUSPENSION ORA	--	0	0	100	0	100	--	0	--	0

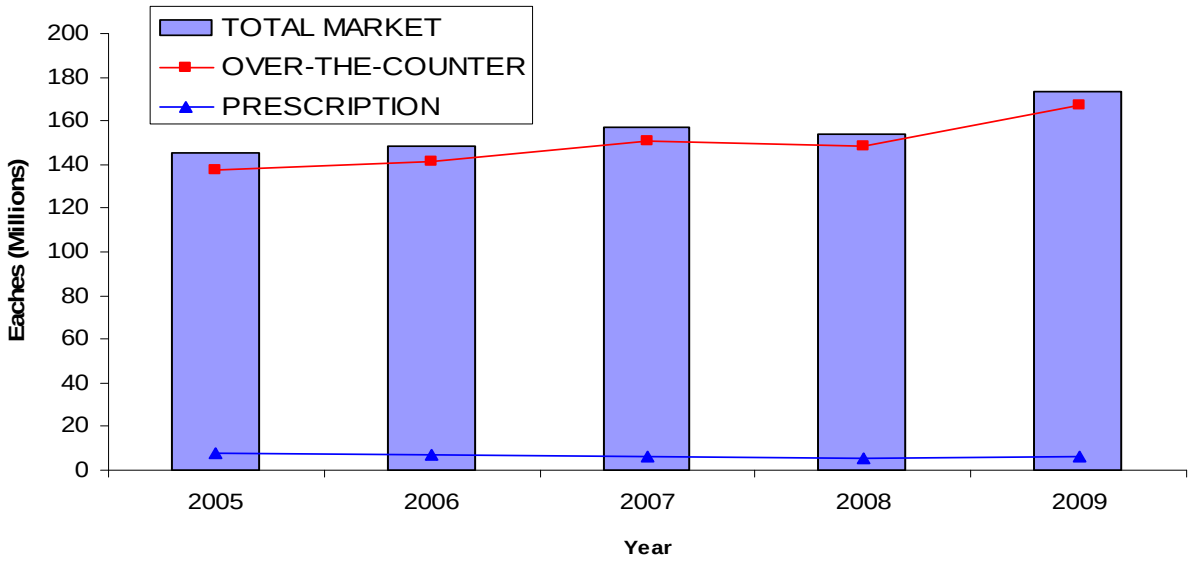
IMS Health. IMS National Sales Perspective™. Years 2005-2009. Extracted July 2010. File: 1007dex3 dvr

*Retail channels include chain, independent, foodstore, mail order, discount house, and mass merchandise pharmacies in the entire United States.

**Non-retail channels include hospitals, long-term care facilities, clinics, home healthcare providers, and HMOs in the entire United States.

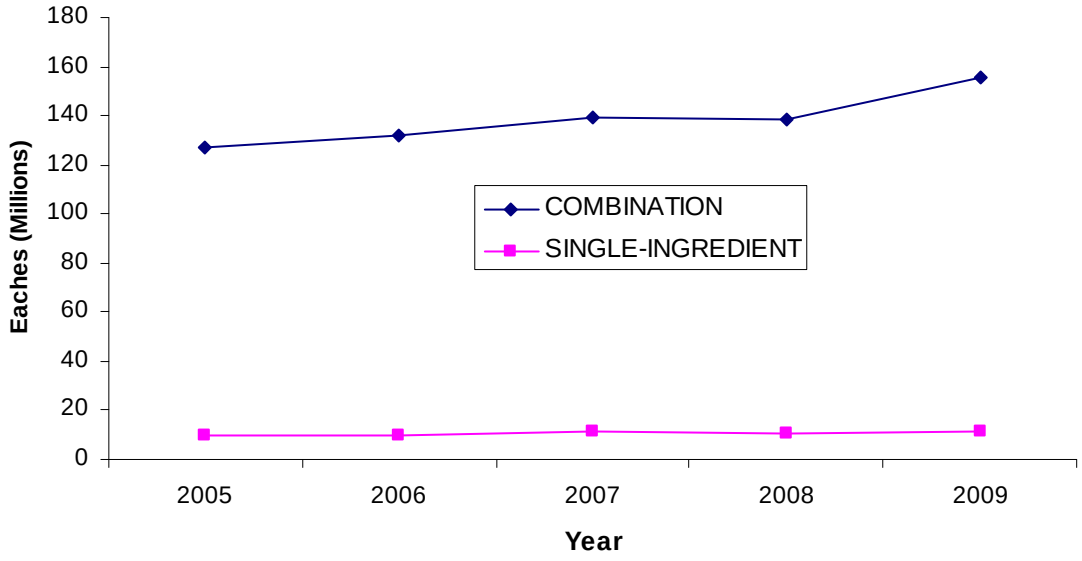
***Eaches refer to the number of packages, bottles.

Figure 1. Total Sales of Over-the-Counter and Prescription Dextromethorphan Products from Manufacturers to Retail and Non-Retail Channels of Distribution, Years 2005-2009



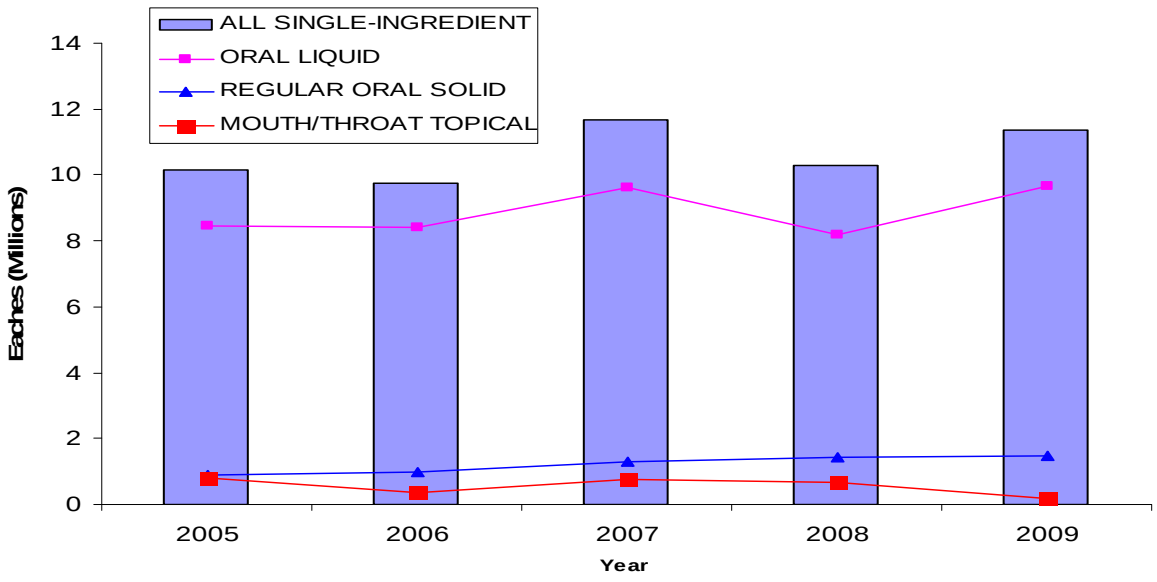
IMS Health. IMS National Sales Perspective™. Years 2005-2009. Extracted July 2010. File: 1007dex3.dvr

Figure 2. Total Sales of Over-the-Counter Dextromethorphan Products, Years 2005-2009



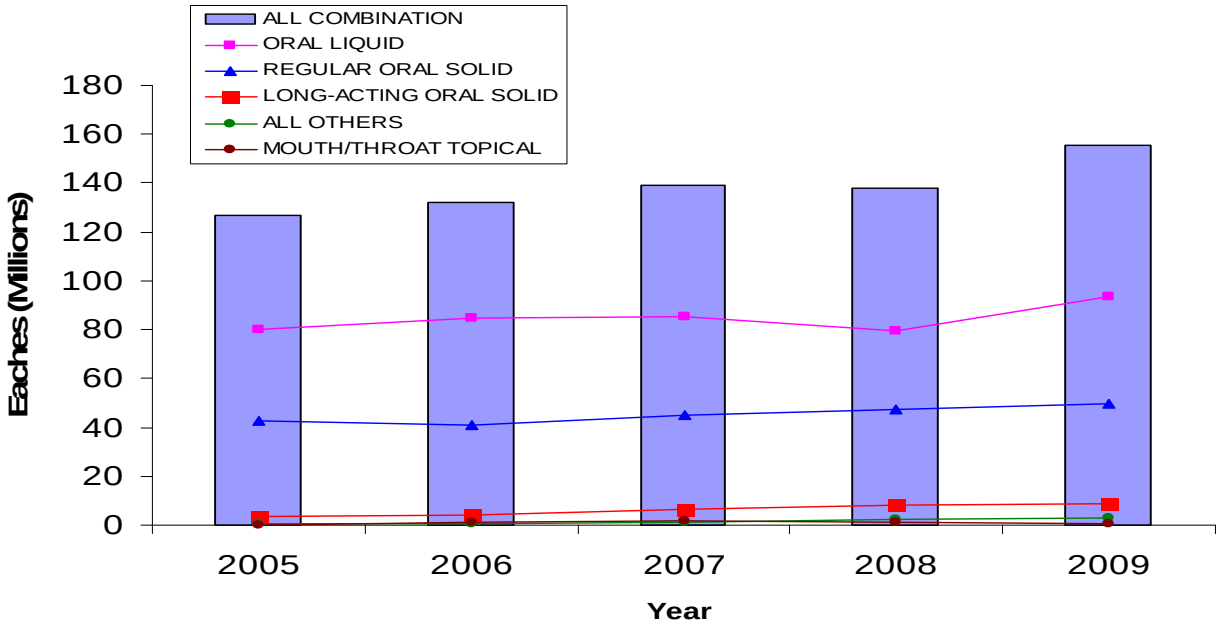
IMS Health. IMS National Sales Perspective™. Years 2005-2009. Extracted July 2010. File: 1007dex3.dvr

Figure 3. Sales of Over-the-Counter Single-Ingredient Dextromethorphan Products by Dosage Forms, Years 2005-2009



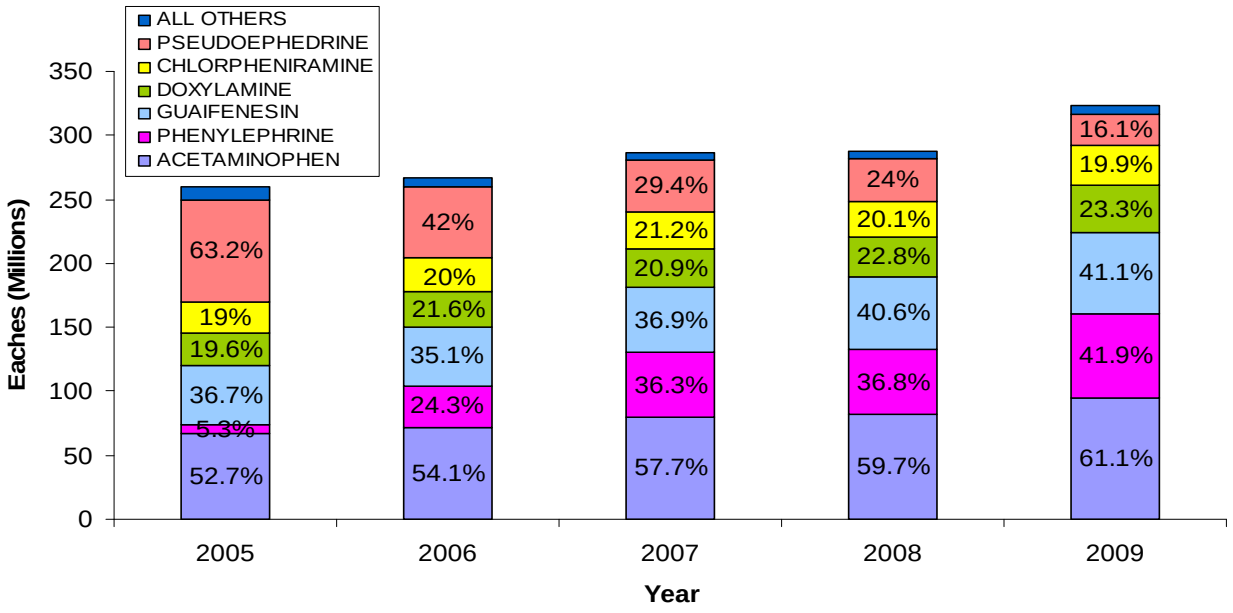
IMS Health. IMS National Sales Perspective™. Years 2005-2009. Extracted July 2010. File: 1007dex3.dvr

Figure 4. Sales of Over-the-Counter Combination Dextromethorphan Products by Dosage Forms, Years 2005-2009



IMS Health. IMS National Sales Perspective™. Years 2005-2009. Extracted July 2010. File: 1007dex3.dvr

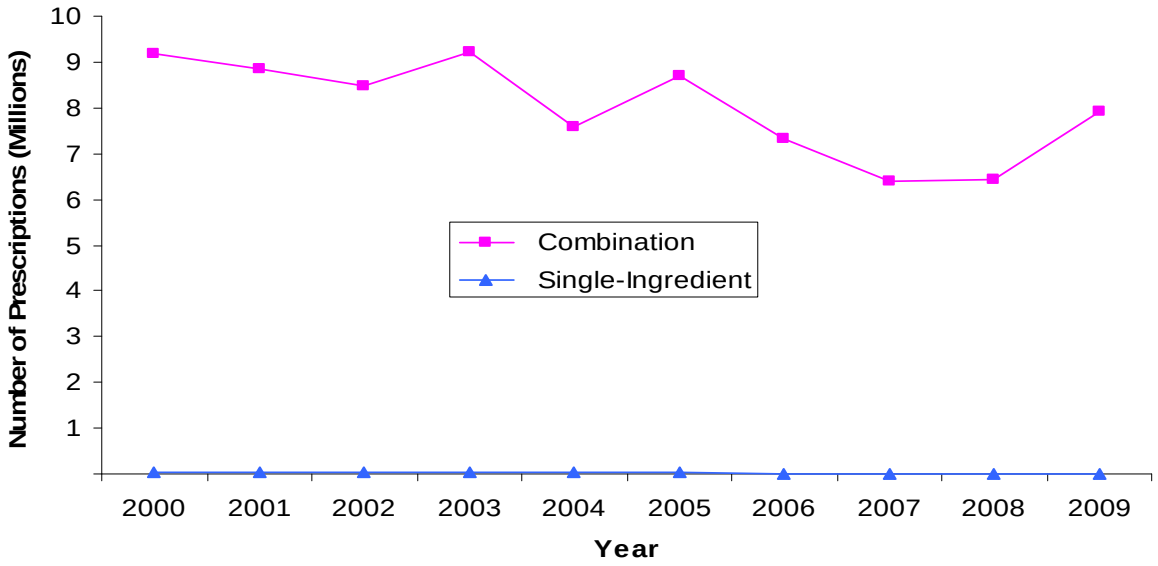
Figure 5. Sales of Over-the-Counter Combination Dextromethorphan Products by Top 6 Ingredients, Years 2005-2009



IMS Health. IMS National Sales Perspective™. Years 2005-2009. Extracted July 2010. File: 1007cou2.dvr

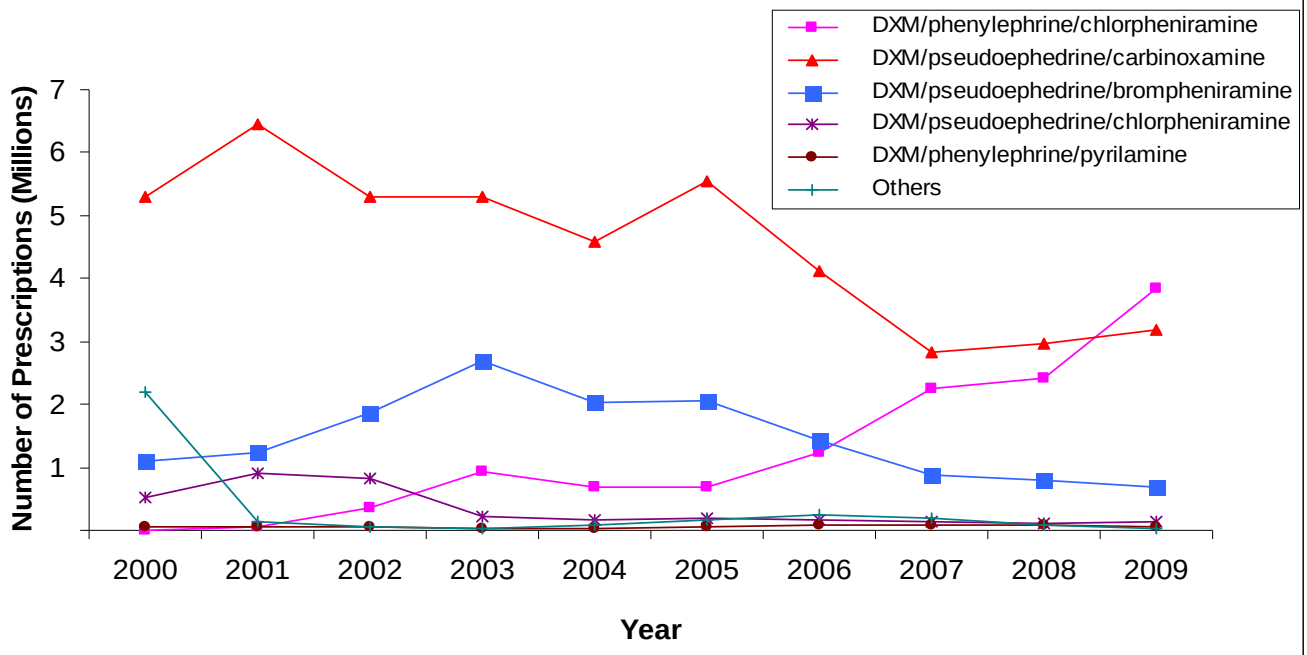
*Percentages do not add up to 100% due to multiple active ingredients being found in combination dextromethorphan products

Figure 6. Projected Number of Outpatient Dispensed Prescriptions for Dextromethorphan Products, Years 2000-2009



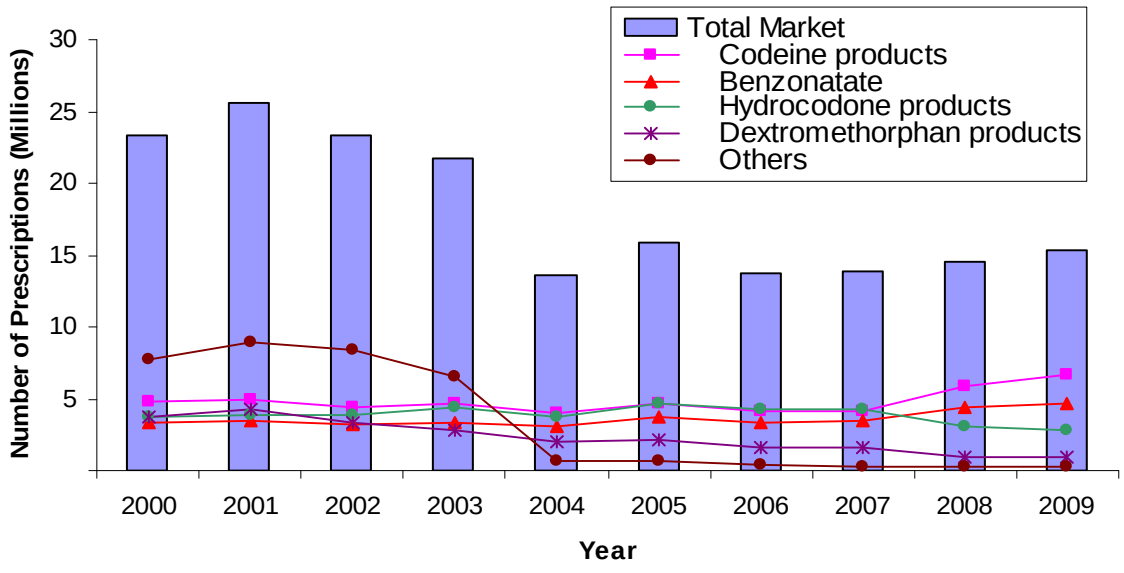
SDI: Vector One®: National. Extracted July 2010. File: VONA 2010-783 DXM Molecule 2000-2009 7-26-10.xls

Figure 7. Projected Number of Outpatient Dispensed Prescriptions for Combination Dextromethorphan Products by Ingredients, Years 2000-2009



SDI: Vector One®: National. Extracted July 2010. File: VONA 2010-783 DXM Molecule 2000-2009 7-26-10.xls

Figure 8. Projected Number of Outpatient Dispensed Prescriptions for Cough/Cold Products, Years 2000-2009



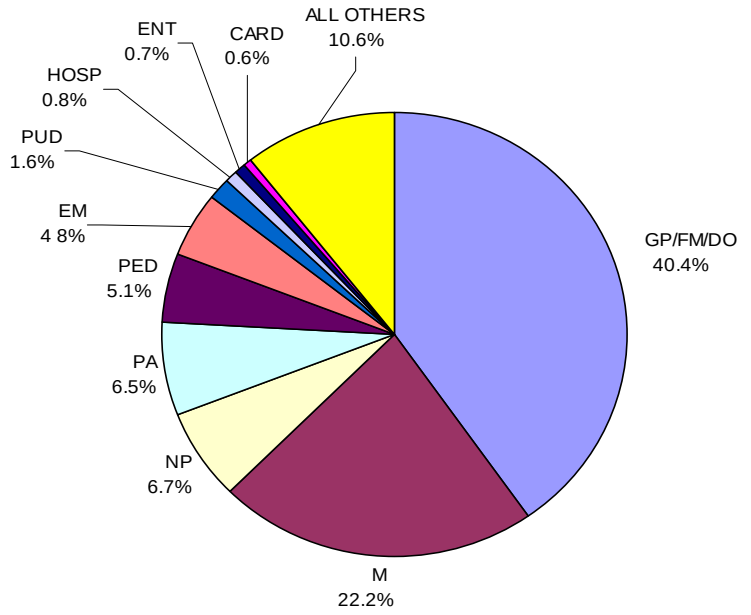
SDI: Vector One®: National. Extracted July 2010. File: VONA 2010-783 cough products 7-20-10.xls

Table 2. Total Number of Dispensed Prescriptions for Cough/Cold Products Class by Prescribing Specialties, Year 2009

	2009 TRxs	2009 Share% TRxs
Total Market	15,380,534	100.0%
GP/FM/DO	6,212,651	40.4%
Codeine products	2,767,307	44.5%
benzonatate	1,912,848	30.8%
Hydrocodone products	1,182,994	19.0%
Dextromethorphan products	272,096	4.4%
Others	77,407	1.2%
IM	3,413,551	22.2%
Codeine products	1,518,241	44.5%
benzonatate	1,035,612	30.3%
Hydrocodone products	640,662	18.8%
Dextromethorphan products	174,670	5.1%
Others	44,365	1.3%
NP	1,027,039	6.7%
Codeine products	480,185	46.8%
benzonatate	350,553	34.1%
Hydrocodone products	135,336	13.2%
Dextromethorphan products	43,537	4.2%
Others	17,429	1.7%
PA	992,579	6.5%
Codeine products	488,463	49.2%
benzonatate	302,880	30.5%
Hydrocodone products	145,470	14.7%
Dextromethorphan products	42,802	4.3%
Others	12,963	1.3%
PED	789,169	5.1%
Codeine products	404,083	51.2%
Dextromethorphan products	165,148	20.9%
benzonatate	130,472	16.5%
Hydrocodone products	55,377	7.0%
Others	34,091	4.3%
EM	744,562	4.8%
Codeine products	287,488	38.6%
benzonatate	223,692	30.0%
Hydrocodone products	207,771	27.9%
Dextromethorphan products	19,748	2.7%
Others	5,863	0.8%
PUD	245,544	1.6%
benzonatate	89,906	36.6%
Hydrocodone products	79,401	32.3%
Codeine products	66,995	27.3%
Others	4,622	1.9%
Dextromethorphan products	4,619	1.9%
HOSP	124,453	0.8%
benzonatate	52,107	41.9%
Codeine products	45,238	36.3%
Dextromethorphan products	11,792	9.5%
Hydrocodone products	10,060	8.1%
Others	5,256	4.2%
ENT	106,366	0.7%
benzonatate	44,461	41.8%
Hydrocodone products	28,745	27.0%
Codeine products	25,181	23.7%
Others	4,406	4.1%
Dextromethorphan products	3,572	3.4%
CARD	94,947	0.6%
Codeine products	37,461	39.5%
benzonatate	28,014	29.5%
Hydrocodone products	23,195	24.4%
Dextromethorphan products	4,834	5.1%
Others	1,443	1.5%
ALL OTHERS	1,629,674	10.6%
Codeine products	315,364	19.4%
benzonatate	249,379	15.3%
Hydrocodone products	216,893	13.3%
Dextromethorphan products	56,103	3.4%
Others	22,274	1.4%

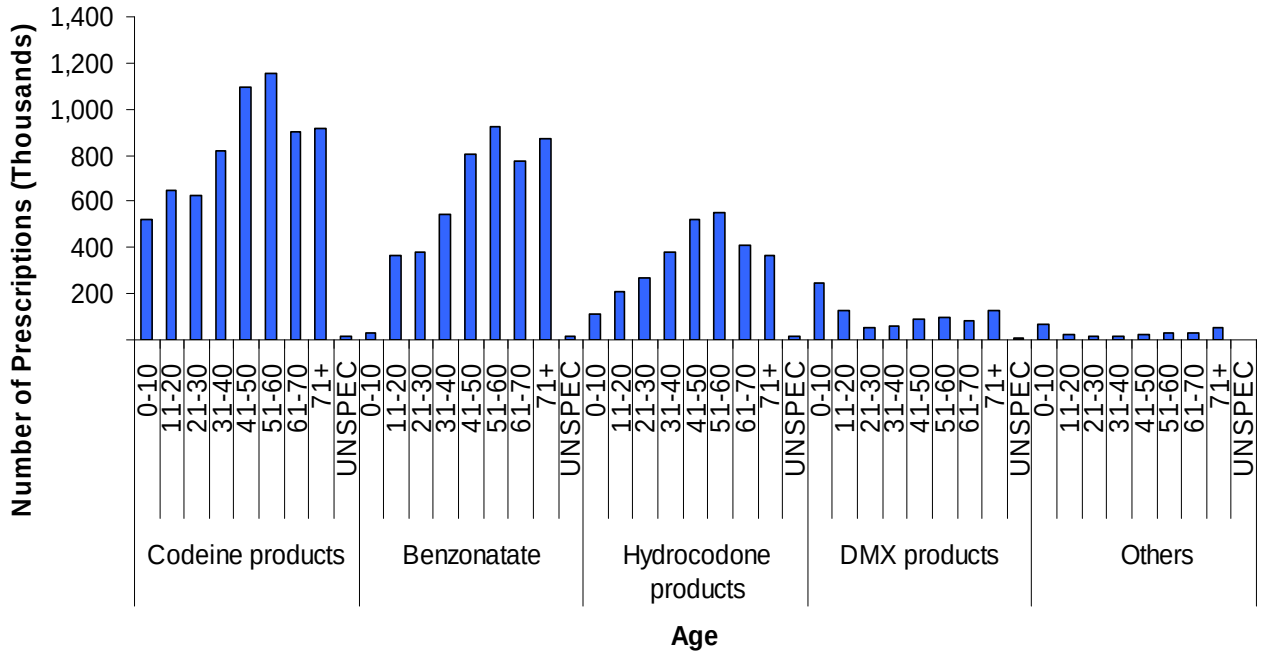
Source: SDI: Vector One®: National. Extracted July 2010.
File: VONA 2010-783 cough products specialties 7-30-10.xls

Figure 9. Market Share Percentage of Outpatient Dispensed Prescriptions for Cough/Cold Products Class by Prescribing Specialties, Year 2009



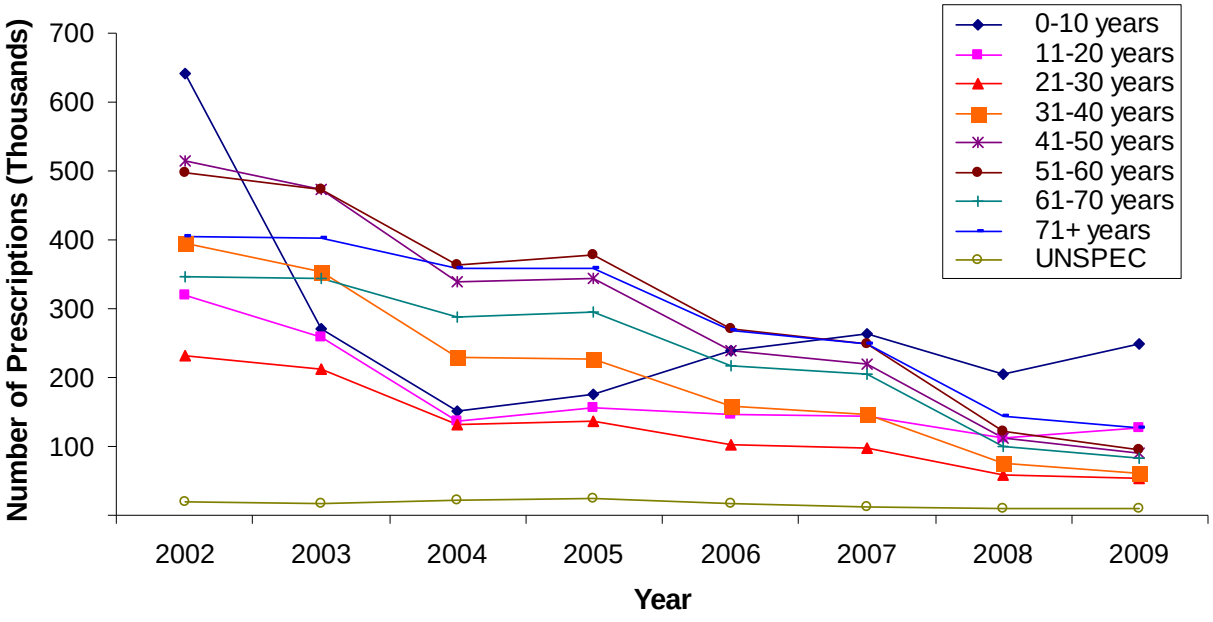
SDI: Vector One®: National. Extracted July 2010. File: VONA 2010-783 cough products specialties 7-30-10.xls

Figure 10. Total Number of Dispensed Prescriptions for Cough/Cold Products by Age, Year 2009



SDI: Vector One®: National. Extracted July 2010. File: VONA 2010-783 cough products age 7-20-10.xls

Figure 11. Total Number of Dispensed Prescriptions for Dextromethorphan Containing Products by Age, Years 2002-2009



SDI: Vector One®: National. Extracted July 2010. File: VONA 2010-783 cough products age 7-20-10.xls

APPENDIX 2: DATABASES DESCRIPTION

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

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

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

APPENDIX 3: UNIFORM SYSTEM OF CLASSIFICATIONS (USC3) FOR OVER-THE-COUNTER COMBINATION DEXTROMETHORPHAN PRODUCTS BY ACTIVE INGREDIENTS[7]

34500 Non-Narcotic Cough Combination Without Expectorant

Dextromethorphan
Acetaminophen
Phenylephrine
Doxylamine
Chlorpheniramine
Pseudoephedrine
Diphenhydramine
Brompheniramine
Guaifenesin
Ascorbic acid
Promethazine
Acetylsalicylic acid
Carbetapentane
Pyrilamine
Dexchlorpheniramine
Codeine
Carbinoxamine
Methscopolamine
Chlophedianol
Dexbrompheniramine

34400 Non-Narcotic Cough Alone

Dextromethorphan
Phenylephrine
Chlorpheniramine
Benzocaine
Glycerol

84100 Homeopathic Products

Dextromethorphan
Phenylephrine

34600 Non-Narcotic Cough Combination with Expectorant

Dextromethorphan
Guaifenesin
Phenylephrine
Acetaminophen
Chlorpheniramine
Pseudoephedrine
Diphenhydramine
Guaiacol sulfonate
Brompheniramine
Citric acid
Potassium

14500 Combination with Expectorant

Dextromethorphan
Guaifenesin
Pseudoephedrine
Phenylephrine
Acetaminophen
Chlorpheniramine
Methscopolamine

14300 Combination with Expectorant

Dextromethorphan
Phenylephrine
Acetaminophen
Pseudoephedrine
Chlorpheniramine
Doxylamine

[7] IMS Health, IMS Natinoal Sales Perspectives™: Year 2009. Extracted July 2010. File: 1007usc3.dvr

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

AERS Date Extracted from Memo (OSE-RCM # 2009-1759) of 12/1/2009

Date: December 1, 2009

To: Michael Klein, Ph.D.
Controlled Substance Staff, HFD-009

Through: Solomon Iyasu, M.D., M.P.H., Director,
Division of Epidemiology, HFD-410

From: Catherine Dormitzer, Ph.D., MPH, Epidemiologist
Division of Epidemiology, HFD-410

Joslyn Swann, Pharm.D., M.G.A., R.Ph., Safety Evaluator
Division of Pharmacovigilance II, HFD-430

Laura Governale, Pharm.D., MBA, Drug Use Analyst Team Leader
Division of Epidemiology, HFD-410

Subject: Abuse, Misuse, and Overdose

Drug Name: Dextromethorphan-Containing Products

Application Type/Number: Various

Applicant/sponsor: Various

OSE RCM #: 2009-1759

CONTENTS

EXECUTIVE SUMMARY

This review is in response to a consult request made by the Controlled Substance Staff (CSS) for an analysis of adverse events associated with the abuse, misuse, and overdose, and related deaths, of dextromethorphan (DXM). The CSS was asked by the Drug Enforcement Administration (DEA) to conduct an analysis for DXM, which will be used in their considerations of drug scheduling. CSS asked the Office of Surveillance and Epidemiology (OSE) to provide an analysis of data from the Adverse Event Reporting System (AERS) database, drug utilization data, and Drug Abuse Warning Network (DAWN) database from calendar year 2004 through 2008.

The AERS database was searched for all reports of adverse events associated with abuse of DXM from January 1, 2004 through December 31, 2008. For this AERS search, all products associated with abuse MedDRA terminology and dextromethorphan were identified. The AERS results included products with various combination of ingredients prescription as well as over-the-counter (OTC) products. The focus of this review includes reports of DXM as a single-ingredient or in combination with guaifenesin only. There were 33 cases associated with DXM as single-ingredient products and 17 cases associated with DXM-with-guaifenesin products.

Our analysis of the AERS cases and data mining scores suggest that the use of DXM has been associated with intentional misuse of products for abuse purposes. As reflected by the AERS data, reports of abuse associated with DXM, whether as single-ingredient or in combination with guaifenesin, significantly increased in 2008. Because of the drug's perceived safety, ease of availability, and desired psychoactive effects, it is sought after by those seeking to alter their mental state or to get "high". Therefore, routine labeling changes or product packaging redesign will probably not reduce the present abuse trend.

As reflected by the AERS case series and data mining analysis, DXM is associated with abuse. Because of the data sources involved the extent of this abuse can not be determined.

1 INTRODUCTION

This review is in response to a consult request made by CSS for an analysis of AEs associated with abuse, misuse, overdose, and related deaths from DXM. CSS was asked by DEA to provide an analysis of data for consideration in the possible scheduling of DXM. Subsequently, CSS asked OSE to provide an analysis of data from the AERS database, drug utilization data, and the DAWN database from calendar year 2004 through 2008.

DXM, a non-narcotic antitussive, is used for the temporary relief of coughs caused by minor throat and bronchial irritation such as may occur with common colds or with inhaled irritants.[1] DXM is most effective in the treatment of chronic, nonproductive cough. It is a common ingredient available in over 100 OTC cold medications either

[1] Dextromethorphan Hydrobromide. AHFS Drug Information® (2009), online. Available at: http://online.statref.com. Accessed: November 2009.

alone or in combination with other drugs such as analgesics (e.g. acetaminophen), antihistamines (e.g. chlorpheniramine), decongestants (e.g. pseudo- ephedrine) and/or expectorants (e.g. guaifenesin).[1,2]

1.1 BACKGROUND

DXM is the d-isomer of levomethorphan, a semisynthetic morphine derivative.[2] It is an analog of the opiate family but retains only the antitussive activity of other morphinan derivatives; it lacks analgesic and addictive properties.[2,3] The drug is about equal to codeine in suppressing the cough reflex and has no expectorant action.[1] Its cough suppressant action is due to a central action on the cough center in the medulla. DXM is rapidly absorbed in the GI tract and exerts its effect in 15-30 minutes after oral administration; its duration of action is approximately 3-6 hours with conventional dosage forms.[1] Once in the body, the drug undergoes metabolism in the liver and is then excreted in the urine as unchanged drug and demethylated metabolites.[3]

Though DXM abuse has been recognized since the 1960s, the drug's misuse has become more common.[4] The drug is abused by individuals of all ages, but its abuse by teenagers and young adults is of particular concern.[2] Reported reasons for this increase include its low cost (a single box/bottle of an OTC product can be a "dose"), easy availability via OTC status, lack of suspicion, and perception that legitimate OTC products must be safe. In addition, various Web sites advertise "how-to" guides for DXM abuse and sales.[2,4,5] Recreational users intentionally exceed approved, recommended doses to experience a sense of heightened perceptual awareness, altered time perception, and/or visual hallucinations.[2]

Abuse of combination DXM products can also result in health complications from the other active ingredient(s), including increased blood pressure from pseudoephedrine, potential delayed liver damage from acetaminophen, and central nervous system toxicity, cardiovascular toxicity and anticholinergic toxicity from antihistamines.[2] The use of high doses of DXM in combination with alcohol or other drugs is particularly dangerous and deaths have been reported.[2] Users seeking to avoid these unwanted effects, often turn to the Internet or illicit sales of pure DXM powder. But these sources pose additional risks including uncertainty of composition, dose, and adulteration with other illicit drugs such as ecstasy and/or methamphetamine.[1,4]

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[2] DEA. Drugs and Chemicals of Concerns: Dextromethorphan. Department of Justice/Drug Enforcement Administration, online. Available at: http://www.deadiversion.usdoj.gov/drugs_concern/dextro_m/dextro_m htm. Accessed: November 2009.

[3] Dextromethorphan Hydrobromide: Actions. Facts and Comparisons® 4.0, online. Available at: http://online factsandcomparisons.com. Accessed: November 2009.

[4] Soller RW. OTC Medicines Corner: DM Abuse In Teens: A Continuing and Increasing Problem. APhA DRUGInfoLINE®. Available at: http://online.statref.com. Accessed: November 2009.

[5] CESAR. Dextromethorphan (DXM). University of Maryland/Center for Substance Abuse Research, online. Available at: http://www.cesar.umd.edu/cesar/drugs/dxm.asp. Accessed: November 2009.

When used at recommended dosages, DXM is a safe and effective cough suppressant with minimal adverse effects. However, the drug can have euphoric, stimulant, and dissociative effects at higher dosages.[1] One metabolite of DXM is dextrorphan, and in high doses it has similar pharmacologic effects as phencyclidine and ketamine.[4] While DXM is abused for its euphoric and dissociative effects, its misuse can result in serious AEs, including death.[1]

DXM has a low order of toxicity, with the potential for toxic effects following acute overdosage being low. However, the presentation of DXM intoxication depends on the ingested dose.[1] Manifestations following acute overdose of DXM may include nausea, vomiting, drowsiness, dizziness, blurred vision, nystagmus, ataxia, shallow respiration, urinary retention, stupor, toxic psychosis, seizures, and coma.[1] Manifestations of minimal intoxication may include tachycardia, hypertension, vomiting, mydriasis, diaphoresis, nystagmus, euphoria, loss of motor coordination, and giggling/laughing. At moderate intoxication signs may also include hallucinations and a plodding ataxic gait ("zombie-like" walking). Severely intoxicated individuals may be agitated or somnolent.[1]

DXM is neither a controlled substance nor a regulated chemical under the Controlled Substances Act (CSA).[2] The CSA specifically excluded DXM from any of the schedules in 1970 because of a lack of significant opiate-like abuse potential. However the CSA provided that DXM could in the future be added as a controlled substance through the traditional scheduling process if warranted.[2] In the pharmaceutical market, products containing DXM are regulated by requirements under a new drug application (NDA) and the OTC monograph.

1.2 PRODUCT LABELING

Delsym® (dextromethorphan polistirex) is currently the only single-ingredient OTC product marketed under an NDA in the United States. It was approved on October 8, 1982, under NDA 018658; the sponsor is Reckitt Benckiser. It is marketed as an oral extended release suspension, equivalent to 30mg of dextromethorphan hydrobromide in each 5 ml.[6]

OTC monograph products containing the antitussive active ingredient dextromethorphan or dextromethorphan hydrobromide are regulated by the Code of Federal Regulations Title 21 Part 341, Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-The-Counter Human Use.[7]

See Appendix 1 for product labeling as related to Delsym® and OTC monograph regulated products.

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[6] Drug Details for Delsym® (NDA 018658/S-026). Approved October 8, 2009. Drugs@FDA, online. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed: November 2009.

[7] Dextromethorphan. Final Monograph (21 CFR part 341): Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm. Accessed: November 2009.

2 ANALYSES OF AERS DATA

2.1 AERS CRUDE COUNTS

The AERS database was searched for all reports of AEs associated with abuse of DXM from January 1, 2004 through December 31, 2008. DXM is a non-narcotic antitussive, available as a single-ingredient and in combination with other ingredients, especially guaifenesin. Therefore, for this AERS search, all reports associated with abuse MedDRA terminology and DXM-containing products were identified.

For purposes of this review, the Preferred Terms (PT) listed below in section 2.1 ***Search Criteria for AERS Crude Counts*** are interchangeable and hereafter are collectively termed 'abuse'.

Search Criteria for AERS Crude Counts

Drug Name: dextromethorphan and all associated salts

Drug Role: Suspect

Report Geographic Location: Domestic and Foreign

Search Date: January 1, 2004 through December 31, 2008

MedDRA Terms: Dependence (PT)

Drug Abuse (PT)

Drug Abuser (PT)

Drug Dependence (PT)

Intentional Drug Misuse (PT)

Intentional Overdose (PT)

Intentional Self-Injury (PT)

Multiple Drug Overdose (PT)

Multiple Drug Overdose Intentional (PT)

Overdose (PT)

Polysubstance Dependence (PT)

Substance Abuse (PT)

Results for AERS Crude Counts

Crude counts may include duplicate AERS reports. The reported AEs may not be directly related to the suspected DXM-containing product. In this section, individual review of each report was not performed to determine an association between the reported abuse event and the use of DXM. In addition, the AERS results may include products with various combination of ingredients; prescription as well as OTC products.

Table 1 below shows the Crude Counts of all AERS reports associated with an Abuse-related adverse event, a serious outcome, death, or hospitalization and DXM, stratified by age groups.

Table 1: Crude Counts[1] of AERS reports associated with Abuse and DXM, Stratified by Age Groups
AERS Search Period: January 1, 2004 through December 31, 2008

Age	All reports	Serious[2]	Deaths	Hospitalization
1 mo < 2 yrs	12	11	10	0
2–5 yrs	7	7	3	3
6–11 yrs	5	5	0	4
12–16 yrs	13	13	2	3
17–20 yrs	34	32	16	8
21–30 yrs	46	46	14	19
31–40 yrs	25	25	15	6
41–50 yrs	27	27	23	2
51–60 yrs	10	10	8	2
61–70 yrs	3	3	3	0
71–80 yrs	4	4	3	1
Unknown	44	43	5	5
Total	**230**	**226**	**102**	**53**
(Percent of Total)		***(98.3%)***	***(44.3%)***	***(23.0%)***

[1] Crude counts may include duplicate reports. The reported adverse events may not be directly related to the suspected DXM-containing product.
[2] Adverse events with a serious outcome per regulatory definition, includes death, hospitalization, life-threatening, disability, congenital anomaly, and other (serious).

There are 230 crude reports, of which approximately 98% (n=226) were reported as serious and 44% (n=102) of all reports had a death outcome. The highest numbers of crude reports (n=46 or 20%) were in the 21–30 years age group; however, the highest percentage of deaths, by age group, was reported in the 41–50 and 1mo<2yr age groups at 85% (n=23) and 83% (n=10) respectively.

The analysis of crude reports showed 13 deaths in children ages 1mo–5 years. Even though these reports are part of the crude count analysis, an individual review was performed on each report because of the associated fatal outcomes. This resulted in six duplicates and 7 unique cases. (See Appendix 2, Table 2 for Line-Listing Description of Fatal Pediatric Cases, ages 1mo–5 years, identified in the Crude Count Analysis for Abuse and DXM). While pediatric adverse events, including those resulting in death, are not germane to this review, we note that they were included in an OSE review prepared for a Joint meeting with the Nonprescription Drugs Advisory Committee and the

Pediatric Advisory Committee on Cold, Cough, Allergy, Bronchodilator, Antiasthmatic Drug Products for Over-the-Counter Human Use in October 2007.[8] The safety concerns of dextromethorphan use in children are being addressed in a larger context of nonprescription cough and cold medicine use in children.

Figure 1 below shows the numbers of crude AERS reports for all abuse-related AEs and deaths associated with DXM for the past five calendar years (2004 through 2008). The crude number of all AE reports peaked sharply in year 2008, with 107 abuse reports including 45 deaths.

Table 3 below lists the Top 20 PTs identified from the crude search of AERS reports associated with Abuse and DXM. The two PTs with the highest frequency are 'Overdose' at 28.26 % and 'Drug Abuse' at 23.48%.

[8] Joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee on Cold, Cough, Allergy, Bronchodilator, Antiasthmatic Drug Products for Over-the-Counter Human Use. Briefing Information for October 18 and 19, 2007 Meeting. Available at: http://www fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs. Accessed: November 2009.

Table 3: Top 20 PTs from Crude Counts of AERS reports associated with Abuse and DXM AERS Search Period: January 1, 2004 through December 31, 2008		
PT	**Count of PTs**	**Percent of Total**
Overdose	65	28.26
Drug Abuse	54	23.48
Intentional Overdose	36	15.65
Intentional Drug Misuse	34	14.78
Drug Abuser	31	13.48
Multiple Drug Overdose	31	13.48
Drug Toxicity	27	11.74
Completed Suicide	24	10.43
Serotonin Syndrome	20	8.70
Confusional State	17	7.39
Drug Interaction	16	6.96
Drug Dependence	14	6.09
Multiple Drug Overdose Intentional	13	5.65
Accidental Overdose	11	4.78
Cardiac Arrest	11	4.78
Dysarthria	10	4.35
Hallucination	10	4.35
Lethargy	10	4.35
Respiratory Arrest	10	4.35
Somnolence	10	4.35

2.2 AERS INDIVIDUAL CASE REVIEW

Using the reports identified in the crude search of AERS, a hands-on review was performed on each individual report and duplicates were consolidated. This resulted in the identification of 53 duplicates and 177 cases.

Because DXM is marketed in products as a single-ingredient and with various multiple-ingredients, CSS requested that the focus of this review include reports of DXM as a

single-ingredient or in combination with guaifenesin only. This subgroup of cases was chosen to minimize the potentially contributory effects of other ingredients.

Consequently, each case was classified into one of the following categories:

- DXM-single-ingredient products
- DXM-with-guaifenesin containing products
- DXM-multiple-ingredient containing products
- Could not confirm formulation of reported product

Selection of Case Series

Cases are *included* if they are associated with:

- DXM as single-ingredient product, OR
- DXM-with-guaifenesin containing product, AND
- A temporal relationship between the reported AE and use of the DXM-containing product.

Cases are *excluded* if they are associated with:

- A DXM-multiple-ingredient containing product, OR
- A formulation that could not be confirmed.

Results for Individual Case Review

After adjudication, cases were excluded for the following reasons: products contained multiple-ingredients (43) and could not confirm the product formulation (78). In addition, six cases were excluded because the reports lacked sufficient details for assessment. The remaining cases (N=50) were associated with DXM as single-ingredient products (33) and DXM-with-guaifenesin products (17). Table 4 below lists the Demographic and Case Characteristics of Abuse Cases associated with DXM (N=50), Stratified by Product Ingredients.

Table 4: Demographic and Case Characteristics of Abuse Cases associated with DXM Stratified by Product Ingredients, N=50 AERS Search Period: January 1, 2004 through December 31, 2008		
	Single-Ingredient Products (DXM only) n=33	**DXM and Guaifenesin Containing Products n=17**
Age (years)	n=22	n=10
Range	2-43	15-76
Mean	21.1	35.3
Median	20.0	26.0
Age Distribution (years)	n=22	n=10
1 mo < 2	1	-
12–16	5	2
17–20	6	3
21–30	8	-
31–40	1	2
41–50	1	-
51–60	-	1
61–70	-	1
71–80	-	1
Unknown	11	7
Gender	n=32	n=11
Female	11	4
Male	21	7
FDA Receipt Year	2004 (2), 2005 (3), 2006 (6), 2007 (2), 2008 (20)	2004(5), 2005 (1), 2006 (1), 2008 (10)
Report Type	15-Day (29), Direct (4)	15-Day (15), Direct (2)
Reporter	Consumer (31), Healthcare Professional (2)	Consumer (12), Healthcare Professional (5)
Report Location	Domestic (30), Foreign (3)	Domestic (17)
Reported Patient Outcome[1]	Died (3), Hospitalized (8), Other (22), Required Intervention (1)	Died (5), Other (11), Required Intervention (1)

[1] Outcomes are not mutually exclusive; a case may be identified more than once.

Eight cases reported a death outcome; these cases included five completed suicides and three overdoses. In the cases of completed suicide, one case also involved a fatal gunshot wound (ISR #: 4424375) and four involved the use of multiple drugs (ISR #s: 4485534, 4472039, 4472043, 4782399). In the overdose cases, two reported use of DXM (ISR #s: 5757361, 5933454) and one involved the use of multiple drugs at the time of death (ISR #: 5933446). Patient ages ranged from 17 to 76 years, the mean and median were 39 and

22 years respectively. The doses associated with the case-reports were not well documented, and length of abuse was not reported at all; drug abuse is associated with acute and chronic activity. (See Appendix 3, Table 5 for Counts of Preferred Terms associated with Abuse and DXM cases and Appendix 4, Table 6 for Line-Listing Description of Cases).

The number of abuse cases in this series increased from seven in 2004 to 30 reports in 2008. The majority of cases were reported by consumers (86.0%) and submitted as expedited 15-day reports (88.0%). In addition, the majority of cases were reported within the U.S. (94.0%).

In this case series, the most frequently reported products containing only DXM were Robitussin Cough Long Acting (27.5%) followed by Delsym (19.6%). Of the products which contained DXM and guaifenesin, the most commonly reported product was Robitussin DM (17.6%). (See Appendix 5, Table 7 for Counts of DXM-Containing Products associated with Abuse).

Select Case Narrative

ISR #: 4330845, Domestic:

A 15 year-old female was found "having hallucinations, was out of it, had difficulty in walking and talking, slurring her speech, could not see well, her eyes were rolling back in her head, and she was afraid she was going to die" by her father after he returned home at approximately 3:00 pm on March 12, 2004. An ambulance was called and the patient was taken to the hospital and admitted. The hospital staff determined that the patient drunk 1-1/2 bottles of Delsym® at approximately 9:00am. Charcoal was administered. At approximately 7:00 pm on March 12, 2004, her symptoms began to abate. While hospitalized, the patient had unspecified physical tests and was psychologically evaluated; results were not reported. In a drug screening, she tested positive for opiates. Her father reported that "the use of Delsym® appeared to be a result of peer pressure and that she may have drank some during the previous week as well." The patient was to be discharged home on March 17, 2004, after six days of hospitalization. The patient was reported to have an uneventful medical history and no concomitant medications were reported.

2.3 DATA MINING ANALYSIS OF AERS DATA

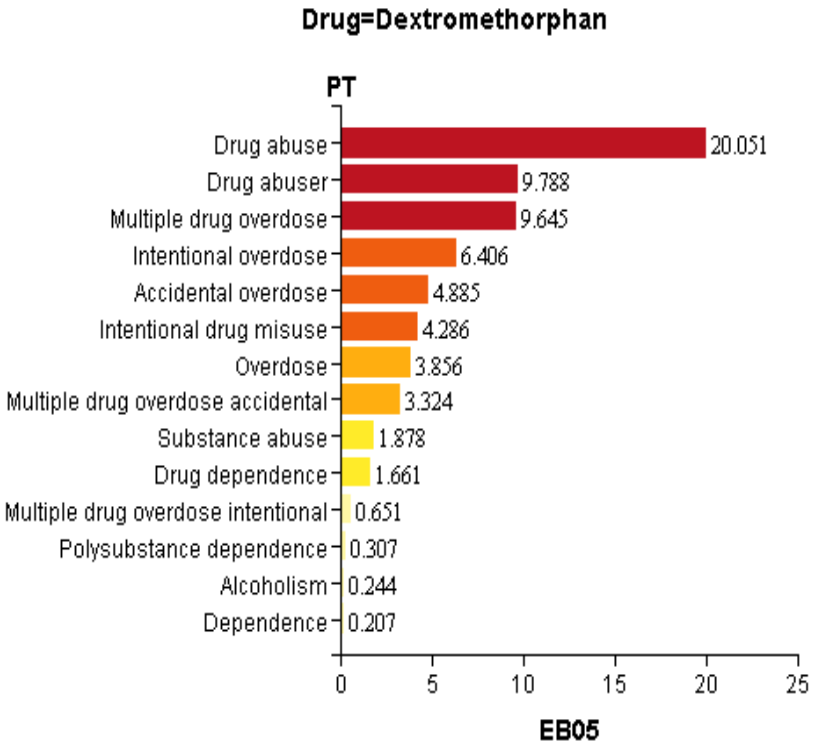
A data mining analysis was also performed on the abuse reports associated with DXM that were submitted to AERS. For this analysis, AERS was searched from the beginning of the database (1969) through November 6, 2009.

This analysis used the Empirica Signal® software and Multi-item Gamma Poisson Shrinker (MGPS)[9,10] data mining algorithm which analyzes records contained in large post-marketing drug safety databases, such as AERS.

[9] DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.

For this data mining analysis, any report associated with a DXM-containing product and one of the following Higher Level Terms (HLT) was identified; these HLTs included Drug and chemical abuse, Overdoses, and Substance-related disorders.

This query determined that the highest drug association was for DXM as a single-ingredient, with 375 crude reports, followed by DXM-with guaifenesin with 45 crude reports. For DXM as a single-ingredient, the highest drug-event combination was represented by an EB05 of 20.051 for 'Drug Abuse', followed by an EB05 of 9.788 for 'Drug Abuser'. This analysis identified a total of 8 drug-event combinations with an EB05 > 2 for DXM as a single-ingredient; each which suggest disproportionate reporting. See bar graph below for DXM as a single-ingredient with associated abuse-related PTs and corresponding EB05 scores.



See Appendix 5 for the bar graph results associated with DXM-containing products, associated abuse-related PTs, and corresponding EB05 scores, from 1969 through November 6, 2009, and Appendix 7, Table 8 for Drug-Event combinations associated

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[10] Szarfman A, Machado SG, O'Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392.

with DXM-containing products and abuse-related PTs, including the count PTs and the corresponding EB05, EBGM, and EB95 scores for the same time period.

2.4 AERS DISCUSSION AND CONCLUSION

Limitations to quantitatively analyzing a spontaneous reporting database such as AERS include use of concomitant medications (which can make establishing a clear drug-event association difficult), absence of a control group for comparison, and underreporting.

A search of the AERS database for cases of abuse-related AEs associated with DXM between 2004 and 2008 resulted in 33 single-ingredient cases and 17 DXM-with-guaifenesin cases. Although reports of serious AEs, including death, have been reported with DXM use, a clear causal drug-event relationship was difficult to establish due to the concomitant use of other medications and limited information provided in many of the case-reports. Because of the drug-seeking behaviors associated with those who desire to get "high", the causal association of other concomitant drugs can not be excluded.

Furthermore, though the specific dose administered may not have been reported, many cases reported doses that exceeded the recommended dosage for single and daily doses. Thirty-one cases (62.0%) involved an overdose of DXM despite labeled warnings not to exceed the recommended dosage. When ingested in doses higher that the recommended ranges, physiological responses of DXM intoxication can manifest. These physiological responses of DXM intoxication, including hallucination, lethargy, euphoric mood, speech disorder, hypertension, irritability, and tachycardia, are consistent with those in the case series, and are biologically plausible based on the pharmacological effects of DXM, especially in overdoses. See Table 3 above for the Top 20 PTs identified from the crude search of AERS reports associated with Abuse and DXM and Appendix 3, Table 5 below for Counts of Preferred Terms associated with Abuse and DXM cases.

An analysis of sales data indicate that the utilization of all OTC DXM containing products has increased approximately 28.3% from year 2004 to year 2007. Purchases of the drug via Internet sales can not be accounted for, although it is known to occur.[2,4,5]

Result from the data mining analysis show that the highest drug association was for DXM as a single-ingredient, and that the highest drug-event combination, represented by an EB05 of 20.051, was 'Drug Abuse', followed by an EB05 of 9.788 for 'Drug Abuser'; EB05 > 2 suggest disproportionate reporting. Results for DXM-with guaifenesin show that 'Drug Abuse' was associated with an EB05 of 6.467.

This AERS review and data mining scores suggest that the use of DXM has been associated with intentional misuse of products for abuse purposes. As reflected by this AERS analysis, reports of abuse associated with DXM, whether as single-ingredient or in combination with guaifenesin, significantly increased in 2008. Because of the drug's perceived safety, ease of availability, and desired psychoactive effects, it is sought after by those seeking to alter their mental state or to get "high".[4] Therefore, routine labeling changes or product packaging redesign will probably not reduce the present abuse trend.

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Criteria used

3 OVERALL CONCLUSION

This review suggests that the use of DXM has been associated with intentional misuse of products for abuse purposes. As reflected by the AERS case series and data mining analysis, DXM is associated with abuse. Because of the data sources involved the extent of this abuse can not be determined.

APPENDICES

APPENDIX 1: PRODUCT LABELING

Under NDA 018658 for Delsym®[6]

Active Ingredient (in each 5 ml):
Dextromethorphan polistirex equivalent to 30 mg of dextromethorphan hydrobromide

Purpose:
Cough suppressant

Uses:
Temporarily relieves:
- cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants
- the impulse to cough to help you get to sleep

Warnings:
Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Directions:
- Shake bottle well before use
- dose as follows or as directed by a doctor

AGE (YEAR)	DOSE
Adults and children 12 years of age and over	10 ml every 12 hours not to exceed 20 ml in 24 hours
Children 6 to under 12 years of age	5 ml every 12 hours not to exceed 10 ml in 24 hours
Children 4 to under 6 years of age	2.5 ml every 12 hours not to exceed 5 ml in 24 hours
Children under 4 years of age	Do not use

Other Information:

- each 5 ml contains: sodium 7 mg.
- store at 20°-25°C (68°-77°F)
- Look for Delsym, now with dosing cup included

Drug Interaction Precaution:
Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Under the OTC monograph[7]

Indications:
"Nonnarcotic cough suppressant for the temporary" (select one of the following: "alleviation," "control," "decrease," "reduction," "relief," or "suppression") "of cough."

Warnings:
- For oral and topical antitussives labeled for adults or for adults and children under 12 years of age. "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."
- For oral and topical antitussives labeled only for children under 12 years of age. "Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

Directions:
The dosage is equivalent to dextromethorphan hydrobromide.
- Adults and children 12 years of age and over: Oral dosage is 10 to 20 milligrams every 4 hours or 30 milligrams every 6 to 8 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor.
- Children 6 to under 12 years of age: Oral dosage is 5 to 10 milligrams every 4 hours or 15 milligrams every 6 to 8 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor.
- Children 2 to under 6 years of age: Oral dosage is 2.5 to 5 milligrams every 4 hours or 7.5 milligrams every 6 to 8 hours, not to exceed 30 milligrams in 24 hours, or as directed by a doctor.
- Children under 2 years of age: Consult a doctor.

Drug Interaction Precaution:

"Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product."

APPENDIX 2: LINE-LISTING DESCRIPTION OF FATAL PEDIATRIC CASES

AGES 1MO–5 YEARS, IDENTIFIED IN THE CRUDE COUNT ANALYSIS

Table 2 for Line-Listing Description of FATAL Pediatric Cases, ages 1mo–5 years, identified in the Crude Count Analysis for Abuse and DXM; Ordered by ISRNUM, n=7
AERS Search Period: January 1, 2004 through December 31, 2008

ISRNUM	FDA Yr	Age	Gender	Country	Reported adverse events	Reported Cause of Death
4417552	2004	20 months	Male	CA	Brain Oedema, Bronchopneumonia, Hilar Lymphadenopathy, Lymphadenopathy, Metabolic Disorder, Overdose, Pericardial Effusion, Pleural Disorder, Pulmonary Congestion, Pulmonary Haemorrhage, Respiratory Failure	Respiratory failure 2nd to DXM overdose in the presence of bronchopneumonia possibly due to a viral infection
4883158	2006	6 months	Female	US	Listless, Overdose, Pneumonia, Screaming	Unintentional overdose of cold products
5013752	2006	4 years	Male	US	Multiple Drug Overdose	Unintentional overdose of another product
5476953	2007	4 years	Female	US	Lethargy, Cardiac Disorder, Lung Disorder, Multiple Drug Overdose, Pollakiuria, Sluggishness, Somnolence, Tremor, Vomiting	Intentional injury to child - by parent
5913121	2008	3 months	Male	US	Drug Interaction, Encephalopathy, Overdose	Acute encephalopathy
5918282	2008	3 months	Male	US	Overdose, Petechiae, Poisoning, Sudden Infant Death Syndrome	Sudden Infant Death Syndrome
6024244	2008	4 months	Female	US	Drug Toxicity, Intentional Drug Misuse	Malicious intentional dosing

APPENDIX 3: COUNTS OF PREFERRED TERMS ASSOCIATED WITH ABUSE AND DXM

Table 5: Counts of Preferred Terms associated with Abuse and DXM, N=50
AERS Search Period: January 1, 2004 through December 31, 2008

Preferred Terms	Count of PTs	Percentage of Total
Drug Abuse	26	11.3
Intentional Overdose	22	9.6
Overdose	14	6.1
Drug Abuser	9	3.9
Disorientation	8	3.5
Dysarthria	8	3.5
Multiple Drug Overdose Intentional	8	3.5
Abnormal Behaviour	7	3.0
Drug Dependence	7	3.0
Confusional State	6	2.6
Gait Disturbance	6	2.6
Hallucination	6	2.6
Lethargy	6	2.6
Somnolence	6	2.6
Completed Suicide	5	2.2
Hallucination, Visual	5	2.2
Euphoric Mood	4	1.7
Insomnia	4	1.7
Intentional Drug Misuse	4	1.7
Speech Disorder	4	1.7
Thinking Abnormal	4	1.7
Aggression	3	1.3
Cardio-Respiratory Arrest	2	0.9
Cough	2	0.9
Crying	2	0.9
Dependence	2	0.9
Drug Ineffective	2	0.9
Drug Screen Positive	2	0.9
Drug Withdrawal Syndrome	2	0.9
Dyspnoea	2	0.9
Hallucination, Auditory	2	0.9
Hypertension	2	0.9
Irritability	2	0.9

Table 5 continued:

Table 5: Counts of Preferred Terms associated with Abuse and DXM, N=50 AERS Search Period: January 1, 2004 through December 31, 2008		
Preferred Terms	**Count of PTs**	**Percentage of Total**
Multiple Drug Overdose	2	0.9
Mydriasis	2	0.9
Night Sweats	2	0.9
Restlessness	2	0.9
Tachycardia	2	0.9
Vision Blurred	2	0.9
Visual Acuity Reduced	2	0.9
Abdominal Pain Upper	1	0.4
Acne	1	0.4
Alcoholism	1	0.4
Anger	1	0.4
Anorexia	1	0.4
Anxiety	1	0.4
Apathy	1	0.4
Cardiac Disorder	1	0.4
Constipation	1	0.4
Coordination Abnormal	1	0.4
Delusion	1	0.4
Depressed Level Of Consciousness	1	0.4
Depression	1	0.4
Diarrhoea	1	0.4
Dissociation	1	0.4
Drug Interaction	1	0.4
Drug Screen False Positive	1	0.4
Drug Tolerance Increased	1	0.4
Drug Toxicity	1	0.4
Electroencephalogram Abnormal	1	0.4
Elevated Mood	1	0.4
Eye Rolling	1	0.4
Fall	1	0.4
Fear	1	0.4
Feeling Abnormal	1	0.4
Feeling Cold	1	0.4
Feeling Drunk	1	0.4
Feeling Of Relaxation	1	0.4

Table 5 continued:

Table 5: Counts of Preferred Terms associated with Abuse and DXM, N=50 AERS Search Period: January 1, 2004 through December 31, 2008		
Preferred Terms	**Count of PTs**	**Percentage of Total**
General Physical Condition Abnormal	1	0.4
Gun Shot Wound	1	0.4
Hallucination, Tactile	1	0.4
Impaired Driving Ability	1	0.4
Incorrect Dose Administered	1	0.4
Legal Problem	1	0.4
Loss Of Consciousness	1	0.4
Marital Problem	1	0.4
Mental Disorder	1	0.4
Myalgia	1	0.4
No Adverse Event	1	0.4
Off Label Use	1	0.4
Paraesthesia	1	0.4
Paranoia	1	0.4
Poisoning	1	0.4
Psychotic Disorder	1	0.4
Refusal Of Treatment By Patient	1	0.4
Respiratory Arrest	1	0.4
Respiratory Tract Congestion	1	0.4
Road Traffic Accident	1	0.4
Self-Medication	1	0.4
Suicidal Ideation	1	0.4
Suicide Attempt	1	0.4
Swollen Tongue	1	0.4
Theft	1	0.4
Therapeutic Response Unexpected	1	0.4
Unemployment	1	0.4
Vomiting	1	0.4
Weight Decreased	1	0.4
Weight Increased	1	0.4

APPENDIX 4: LINE-LISTING DESCRIPTION OF CASE ASSOCIATED WITH ABUSE AND DXM

Table 6: Line-Listing Description of Case associated with Abuse and DXM
Stratified by Product Classification and Ordered by ISRNUM, N=50
AERS Search Period: January 1, 2004 through December 31, 2008

Classification	ISRNUM	FDA Date	Age	Gender	DXM Product	Outcome	Adverse Events
DXM only	4330845	2004	15	F	Delsym	HO	Intentional Overdose, Hallucination, Eye Rolling, Fear, Visual Acuity Reduced, Dysarthria, Gait Disturbance, Drug Abuser, Drug Screen Positive, Speech Disorder, Abnormal Behaviour
DXM only	4353379	2004	16	M	Delsym	OT	Disorientation, Drug Abuser, Hallucination, Alcoholism, Drug Screen Positive
DXM only	4659504	2005	—	F	Buckley's DM	OT	Drug Abuser, Intentional Drug Misuse, No Adverse Event
DXM only	4665630	2005	29	F	Delsym	HO	Overdose, Disorientation, Dysarthria, Abnormal Behaviour, Hallucination, Auditory, Hallucination, Visual
DXM only	4821931	2005	—	F	Benylin	OT	Abdominal Pain Upper, Crying, Intentional Overdose
DXM only	4885734	2006	24	F	Bexin	HO	Drug Interaction, Suicide Attempt, Multiple Drug Overdose Intentional, Disorientation, Coordination Abnormal, Tachycardia, Gait Disturbance

Table 6 continued:

Table 6: Line-Listing Description of Case associated with Abuse and DXM Stratified by Product Classification and Ordered by ISRNUM, N=50
AERS Search Period: January 1, 2004 through December 31, 2008

Classification	ISRNUM	FDA Date	Age	Gender	DXM Product	Outcome	Adverse Events
DXM only	4918794	2006	21	M	Delsym	HO	Intentional Overdose
DXM only	4934935	2006	18	M	Delsym	RI	Intentional Overdose, Somnolence, Swollen Tongue, Disorientation, Vision Blurred, Drug Abuser
DXM only	4966949	2006	—	F	Delsym	HO	Feeling Abnormal, Irritability, Electroencephalogram Abnormal, Hallucination, Visual, Confusional State, Drug Ineffective, Self-Medication, Overdose
DXM only	4989730	2006	43	M	Delsym	OT	Thinking Abnormal, Abnormal Behaviour, Anger, Anorexia, Insomnia, Weight Decreased, Drug Abuser,
DXM only	5060677	2006	15	M	Dexalone	HO, OT	Intentional Drug Misuse, Incorrect Dose Administered, Hallucination, Depressed Level Of Consciousness
DXM only	5242955	2007	30	M	Delsym	HO	Hallucination, Aggression, Drug Abuser
DXM only	5377102	2007	20	M	Robitussin Maximum Strength Cough Syrup	OT	Fall, Drug Abuser, Impaired Driving Ability, Lethargy, Lethargy, Lethargy, Dysarthria, Dysarthria, Mydriasis, Mydriasis, Off Label Use

Table 6 continued:

Table 6: Line-Listing Description of Case associated with Abuse and DXM Stratified by Product Classification and Ordered by ISRNUM, N=50
AERS Search Period: January 1, 2004 through December 31, 2008

Classification	ISRNUM	FDA Date	Age	Gender	DXM Product	Outcome	Adverse Events
DXM only	5603877	2008	17	M	Robitussin Cough Long Acting	OT	Drug Abuse
DXM only	5614115	2008	—	M	Robitussin Cough Long Acting	OT	Overdose, Drug Abuse, Road Traffic Accident
DXM only	5648552	2008	33	F	Delsym	OT	Overdose, Paraesthesia, Intentional Drug Misuse, Euphoric Mood, Drug Abuse
DXM only	5684193	2008	17	M	Robitussin Cough	OT	Drug Abuse
DXM only	5689159	2008	30	F	Robitussin Cough Long Acting	OT	Overdose, Drug Dependence, Drug Abuse
DXM only	5712369	2008	2	M	Delsym	HO	Vomiting, Hallucination, Visual, Gait Disturbance, Dysarthria, Aggression, Overdose
DXM only	5757361	2008	—	M	Robitussin Cough Long Acting	DE	Overdose
DXM only	5793220	2008	—	F	Robitussin Cough	OT	Intentional Overdose, Drug Dependence
DXM only	5815701	2008	—	F	Robitussin Cough	OT	Overdose, Drug Screen False Positive, Drug Abuse
DXM only	5875969	2008	20	M	Robitussin Cough Long Acting	OT	Intentional Overdose, Drug Abuse, Confusional State, Abnormal Behaviour

Table 6 continued:

Table 6: Line-Listing Description of Case associated with Abuse and DXM Stratified by Product Classification and Ordered by ISRNUM, N=50
AERS Search Period: January 1, 2004 through December 31, 2008

Classification	ISRNUM	FDA Date	Age	Gender	DXM Product	Outcome	Adverse Events
DXM only	5876148	2008	23	M	Robitussin Cough	OT	Intentional Overdose, Drug Abuse, Abnormal Behaviour, Hallucination
DXM only	5926805	2008	—	M	Robitussin Cough Long Acting	OT	Intentional Overdose, Euphoric Mood, Drug Abuse
DXM only	5926812	2008	16	M	Robitussin Cough Long Acting	OT	Overdose, Hallucination, Visual, Hallucination, Auditory, Drug Abuse
DXM only	5926816	2008	15	M	Robitussin Cough Long Acting	OT	Overdose, Drug Toxicity
DXM only	5926822	2008	21	M	Robitussin Cough Long Acting	OT	Drug Abuse
DXM only	5933446	2008	18	M	Robitussin Cough Long Acting	DE	Hallucination, Multiple Drug Overdose, Respiratory Arrest, Drug Abuse, Drug Dependence
DXM only	5933449	2008	—	M	Robitussin Cough Long Acting	OT	Drug Dependence, Intentional Overdose, Dissociation, Elevated Mood, Abnormal Behaviour, Cardiac Disorder, Speech Disorder
DXM only	5933450	2008	—	F	Robitussin Cough Long Acting	OT	Drug Dependence, General Physical Condition Abnormal, Mental Disorder, Refusal Of Treatment By Patient

Table 6 continued:

Table 6: Line-Listing Description of Case associated with Abuse and DXM Stratified by Product Classification and Ordered by ISRNUM, N=50
AERS Search Period: January 1, 2004 through December 31, 2008

Classification	ISRNUM	FDA Date	Age	Gender	DXM Product	Outcome	Adverse Events
DXM only	5933451	2008	—	M	Robitussin Cough Long Acting	OT	Drug Abuse, Aggression, Loss Of Consciousness, Suicidal Ideation
DXM only	5933454	2008	22	—	Robitussin Cough Long Acting	DE	Overdose
DXM and guaifenesin	4286541	2004	—	—	Coricidin Chest Congestion & Cough	RI	Intentional Overdose, Hypertension, Respiratory Tract Congestion, Cough
DXM and guaifenesin	4424375	2004	20	M	Coricidin Chest Congestion & Cough	DE	Gun Shot Wound, Completed Suicide, Drug Abuser, Theft
DXM and guaifenesin	4472039	2004	17	—	Dextromethorphan / Guaifenesin	DE	Completed Suicide, Multiple Drug Overdose Intentional
DXM and guaifenesin	4472043	2004	62	—	Dextromethorphan / Guaifenesin	DE	Completed Suicide, Multiple Drug Overdose Intentional
DXM and guaifenesin	4485534	2004	76	—	Guiatuss DM	DE	Completed Suicide, Multiple Drug Overdose Intentional
DXM and guaifenesin	4782399	2005	60	—	Dextromethorphan / Guaifenesin	DE	Multiple Drug Overdose, Cardio-Respiratory Arrest, Completed Suicide

Table 6 continued:

Table 6: Line-Listing Description of Case associated with Abuse and DXM Stratified by Product Classification and Ordered by ISRNUM, N=50
AERS Search Period: January 1, 2004 through December 31, 2008

Classification	ISRNUM	FDA Date	Age	Gender	DXM Product	Outcome	Adverse Events
DXM and guaifenesin	5034533	2006	38	F	Tussin DM	OT	Psychotic Disorder, Drug Dependence, Drug Withdrawal Syndrome, Poisoning, Intentional Drug Misuse, Paranoia, Delusion, Anxiety, Thinking Abnormal, Thinking Abnormal, Hallucination, Visual, Hallucination, Tactile, Drug Tolerance Increased, Euphoric Mood, Feeling Of Relaxation, Legal Problem, Drug Abuser, Insomnia, Constipation, Weight Increased, Acne, Marital Problem, Unemployment, Night Sweats, Myalgia, Diarrhoea, Restlessness, Feeling Cold
DXM and guaifenesin	5648561	2008	—	M	Robitussin Sugar Free Cough	OT	Drug Abuse
DXM and guaifenesin	5662730	2008	17	M	Robitussin DM	OT	Drug Abuse, Feeling Drunk, Apathy, Somnolence, Abnormal Behaviour
DXM and guaifenesin	5678902	2008	32	F	Robitussin DM	OT	Overdose, Euphoric Mood, Drug Ineffective, Dependence
DXM and guaifenesin	5701023	2008	—	M	Robitussin DM	OT	Overdose, Drug Dependence
DXM and guaifenesin	5746230	2008	—	M	Robitussin DM	OT	Overdose, Drug Abuse

Table 6 continued:

Table 6: Line-Listing Description of Case associated with Abuse and DXM Stratified by Product Classification and Ordered by ISRNUM, N=50
AERS Search Period: January 1, 2004 through December 31, 2008

Classification	ISRNUM	FDA Date	Age	Gender	DXM Product	Outcome	Adverse Events
DXM and guaifenesin	5794758	2008	—	M	Robitussin DM	OT	Drug Abuse
DXM and guaifenesin	5801110	2008	15	M	Robitussin DM	OT	Drug Abuse
DXM and guaifenesin	5811472	2008	—	F	Robitussin DM	OT	Dependence, Therapeutic Response Unexpected, Cough
DXM and guaifenesin	5888240	2008	—	—	Robitussin DM	OT	Drug Abuse
DXM and guaifenesin	5987565	2008	16	F	Robitussin DM, Robitussin Cough and Cold Long Acting	OT	Drug Abuse, Somnolence, Depression, Intentional Overdose

Legend:
Outcomes: DE-died; HO-hospitalized; OT-other; RI-required intervention

APPENDIX 5: COUNTS OF DXM-CONTAINING PRODUCTS ASSOCIATED WITH ABUSE AND DXM

Table 7: Counts of DXM-Containing Products associated with Abuse and DXM Stratified by Product Classification, N=50
AERS Search Period: January 1, 2004 through December 31, 2008

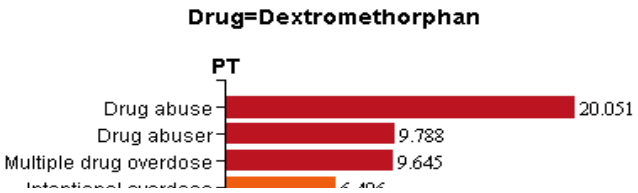
	Product Reported	**Count***	**% Total**
DXM only	Robitussin Cough Long Acting	14	27.5
DXM only	Delsym	10	19.6
DXM only	Robitussin Cough	4	7.8
DXM only	Benylin	1	2.0
DXM only	Bexin	1	2.0
DXM only	Buckley's DM	1	2.0
DXM only	Dexalone	1	2.0
DXM only	Robitussin Maximum Strength Cough Syrup	1	2.0
Sub-totals		**33**	**64.7**
DXM and guaifenesin	Robitussin DM	9	17.6
DXM and guaifenesin	Dextromethorphan / Guaifenesin	3	5.9
DXM and guaifenesin	Coricidin Chest Congestion & Cough	2	3.9
DXM and guaifenesin	Guiatuss DM	1	2.0
DXM and guaifenesin	Robitussin Cough and Cold Long Acting	1	2.0
DXM and guaifenesin	Robitussin Sugar Free Cough	1	2.0
DXM and guaifenesin	Tussin DM	1	2.0
Sub-totals		**18**	**35.3**

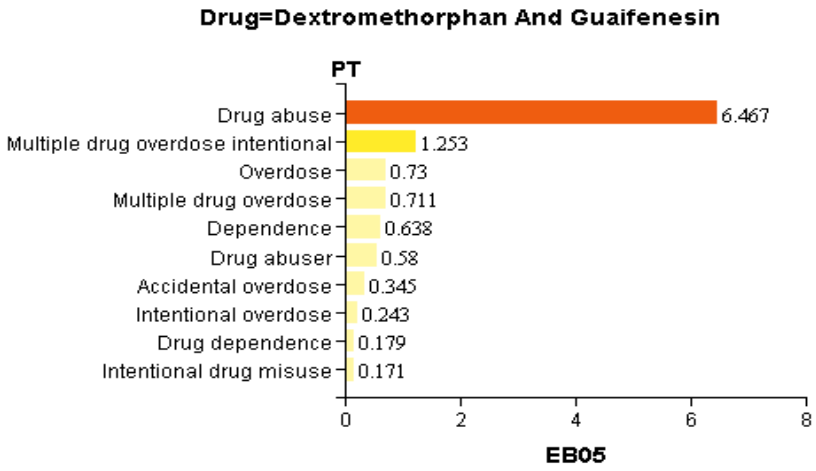
* A case may be associated with more than one product.

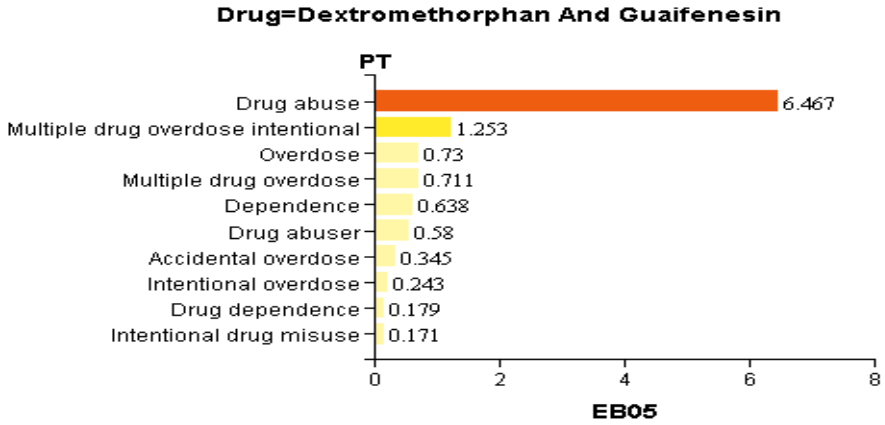
APPENDIX 6: DATA MINING GRAPHS FOR DXM-CONTAINING PRODUCTS AND ABUSE-RELATED PTS

The data mining search resulted in seven bar graphs, one for each identified generic form of DXM and the associated PTs. AERS was searched from 1969 through November 6, 2009. The bar graphs are order by EB05 scores.

As noted below, the highest drug association was for DXM as a single-ingredient, with 375 crude reports, followed by DXM-with guaifenesin with 45 crude reports. In the bar graph of DXM as a single-ingredient, the highest drug-event combination was represented by an EB05 of 20.051 for 'Drug Abuse', followed by an EB05 of 9.788 for 'Drug Abuser'. In addition, this data mining analysis identified 6 other drug-event combinations with an EB05 > 2, which suggest disproportionate reporting. In the bar graph for DXM-with guaifenesin, 'Drug Abuse' was associated with an EB05 of 6.467.

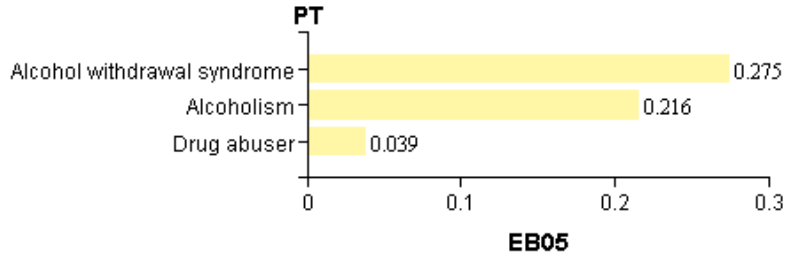




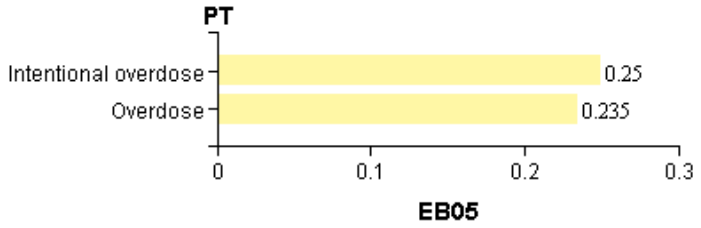


Appendix 6 continued:

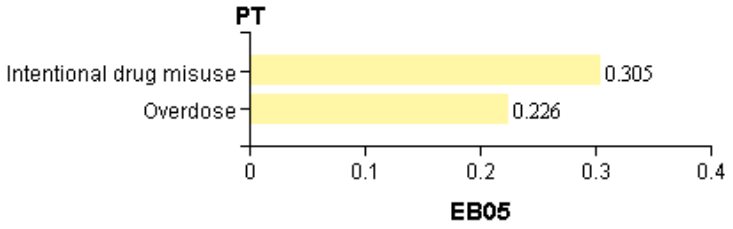
Drug=Dextromethorphan And Guaifenesin And Phenylpropanolamine



Drug=Dextromethorphan And Guaifenesin And Pseudoephedrine

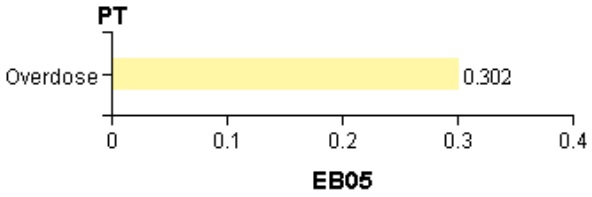


Drug=Dextromethorphan And Phenylephrine

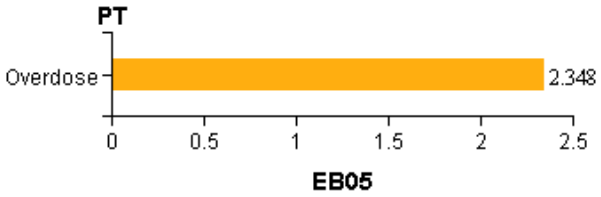


Appendix 6 continued:

Drug=Dextromethorphan And Phenylpropanolamine



Drug=Dextromethorphan And Promethazine



0	≤	EB05	≤	1	<	EB05	≤	2	<	EB05	≤	4	<	EB05	≤	8	<	EB05	<		∞

Source Data: CBAERS data from Extract provided by CBER as of 11/06/2009 00:00:00 loaded on 2009-11-11 00:19:46.0

Note: The sum of the preferred terms does not equal the number of cases elicited because cases may be coded with more than one term. Data mining results do not, by themselves, demonstrate causal associations; they may only serve as a signal for further investigation.

APPENDIX 7: DATA MINING SCORES

DATA ANALYSES FOR DEXTROMETHORPHAN-CONTAINING PRODUCTS AND ABUSE-RELATED HLTS

A data mining analysis of the Adverse Event Reporting System (AERS) database was performed for this review using Empirica Signal® software and the Multi-item Gamma Poisson Shrinker (MGPS)[9,10] data mining algorithm. MGPS quantifies reported drug-event associations by producing a set of values or scores which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database being analyzed. MGPS also calculates lower and upper 90% confidence limits for the EBGM values, denoted EB05 and EB95 respectively.

Table 8 below lists EBGM values and confidence limits for various MedDRA preferred terms (PT) associated with DXM-containing products and abuse-related HLTs in the AERS data. Scores are sorted by EB05 value.

In this analysis, EBGM values indicate the strength of the reporting relationship between a particular drug and event, as reported in AERS. For example, if EBGM=10 for a drug-event combination, then the drug-event occurred 10 times more frequently in the database than statistically expected when considering all other drugs and events in AERS database as a background, the "expected." A drug-event combination having an EB05 > 1 indicates 95% confidence that this drug-event combination occurs at least at a higher-than-expected rate considering all other drugs and events in the database. A drug-event combination having an EB05 ≥ 2 indicates 95% confidence that this drug-event combination occur at least twice the expected rate when considering all other drugs and events in the database.

In addition, the higher the EBGM score (and accompanying EB05, EB95 confidence intervals) for a particular drug-event, the higher the association is between that drug and event, given the database being analyzed. Note that this "association" is a result of the relative reporting for various events among all drugs in the database. The scores discussed in this section provide an indication of the association of AEs with DXM, given the data analyzed. The exact degree of this association (in all patients exposed to the drug worldwide), however, cannot be elicited from an MGPS data mining analysis alone, because obviously the association scores (EBGM values) from such an analysis are generated from the specific database analyzed—in this case AERS which consists of spontaneous AEs reports. It is also important for the reader to understand that an elevated EBGM score of association for a particular drug-event combination does not prove causality or an increased relative risk of that drug-event. Similarly, the absence of an elevated EBGM score for a drug-event cannot be interpreted as a definite lack of toxicity for that drug-event. Finally, reporting and detection biases can occur in AERS and effects of concomitant illnesses or therapy cannot be fully controlled in data mining analyses using MGPS. Because of the spontaneous nature of reporting, the results of this analysis should not be interpreted as a formal comparison of treatment groups or of their relative risks.

Findings: As is noted in Table 8 below, the highest drug association was for DXM as a single-ingredient, followed by DXM-with guaifenesin. For DXM as a single-ingredient, the highest drug-event combination was represented by an EB05 of 20.051 for 'Drug Abuse', followed by an EB05 of 9.788 for 'Drug Abuser'. In addition, this data mining analysis identified 6 other drug-event combinations with an EB05 > 2, which suggest disproportionate reporting. For DXM-with guaifenesin, 'Drug Abuse' was associated with an EB05 of 6.467.

Table 8: Data Mining Results for AERS Reports associated with DXM-containing product and Abuse-Related HLTs Ordered by EB05s

AERS data from 1969 through November 6, 2009

Generic name	PT	N	EB05	EBGM	EB95
Dextromethorphan	Drug abuse	35	**20.051**	26.739	35.079
Dextromethorphan	Drug abuser	38	**9.788**	13.433	17.703
Dextromethorphan	Multiple drug overdose	30	**9.645**	13.962	19.08
Dextromethorphan And Guaifenesin	Drug abuse	7	**6.467**	24.199	49.086
Dextromethorphan	Intentional overdose	66	**6.406**	8.001	9.993
Dextromethorphan	Accidental overdose	66	**4.885**	6.014	7.353
Dextromethorphan	Intentional drug misuse	25	**4.286**	6.088	8.619
Dextromethorphan	Overdose	82	**3.856**	4.637	5.54
Dextromethorphan	Multiple drug overdose accidental	6	**3.324**	14.466	41.18
Dextromethorphan And Promethazine	Overdose	6	**2.348**	5.805	20.623
Dextromethorphan	Substance abuse	6	1.878	3.8	7.326
Dextromethorphan	Drug dependence	15	1.661	2.566	3.822
Dextromethorphan And Guaifenesin	Multiple drug overdose intentional	5	1.253	2.641	5.059
Dextromethorphan And Guaifenesin	Overdose	11	0.73	1.212	1.917
Dextromethorphan And Guaifenesin	Multiple drug overdose	4	0.711	1.624	3.293
Dextromethorphan	Multiple drug overdose intentional	3	0.651	1.668	3.678
Dextromethorphan And Guaifenesin	Dependence	2	0.638	1.974	5.02
Dextromethorphan And Guaifenesin	Drug abuser	4	0.58	1.325	2.686
Dextromethorphan And Guaifenesin	Accidental overdose	3	0.345	0.884	1.948
Dextromethorphan	Polysubstance dependence	1	0.307	1.316	4.114
Dextromethorphan And Phenylephrine	Intentional drug misuse	1	0.305	1.306	4.077
Dextromethorphan And Phenylpropanolamine	Overdose	1	0.302	1.29	4.023
Dextromethorphan And Guaifenesin And Phenylpropanolamine	Alcohol withdrawal syndrome	1	0.275	1.17	3.627
Dextromethorphan And Guaifenesin And Pseudoephedrine	Intentional overdose	1	0.25	1.064	3.292
Dextromethorphan	Alcoholism	1	0.244	1.038	3.209
Dextromethorphan And Guaifenesin	Intentional overdose	3	0.243	0.623	1.372
Dextromethorphan And Guaifenesin And Pseudoephedrine	Overdose	1	0.235	0.999	3.087
Dextromethorphan And Phenylephrine	Overdose	1	0.226	0.962	2.974
Dextromethorphan And Guaifenesin And Phenylpropanolamine	Alcoholism	1	0.216	0.92	2.844
Dextromethorphan	Dependence	1	0.207	0.882	2.727
Dextromethorphan And Guaifenesin	Drug dependence	5	0.179	0.377	0.719
Dextromethorphan And Guaifenesin	Intentional drug misuse	1	0.171	0.729	2.253
Dextromethorphan And Guaifenesin And Phenylpropanolamine	Drug abuser	1	0.039	0.168	0.518

Source Data: CBAERS data from Extract provided by CBER as of 11/06/2009 00:00:00 loaded on 2009-11-11 00:19:46.0

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

Date:	August 13, 2010
To:	Michael Klein, Ph.D. Controlled Substance Staff, HFD-009
Through:	Amarilys Vega, M.D., M.P.H., Deputy Director, Division of Epidemiology, HFD-410
From:	Catherine Dormitzer, Ph.D., MPH, Epidemiologist Division of Epidemiology, HFD-410
	Laura Governale, Pharm.D., MBA, Drug Use Analyst Team Leader Division of Epidemiology, HFD-410
Subject:	Abuse, Misuse, and Overdose
Drug Name:	Dextromethorphan-Containing Products
Application Type/Number:	Various
Applicant/sponsor:	Various
OSE RCM #:	2009-1759

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CONTENTS

EXECUTIVE SUMMARY

This review is in response to a consult request made by the Controlled Substance Staff (CSS) for an analysis of events associated with the abuse, and misuse of dextromethorphan (DXM) as well as for comparator drugs: diphenhydramine, pseudoephedrine, and codeine products that are scheduled as C-V products under the Controlled Substances Act (CSA). The Drug Enforcement Administration (DEA) requested CSS to conduct an analysis for DXM to inform their considerations of drug scheduling. CSS asked the Office of Surveillance and Epidemiology (OSE) to provide an analysis of drug utilization data and data from the Drug Abuse Warning Network (DAWN) database from calendar year 2004 through 2008.

DAWN data provide evidence of drug abuse of DXM single ingredient containing products in the community. However, it does not indicate that DXM products are widely abused. There were close to 2,000 emergency department (ED) visits per year associated with the use of single ingredient DXM products. Approximately half of the ED visits attributed to the use of DXM products were related to abuse and misuse of these products. The number of all misuse/abuse (AllMA) ED visits per 10,000 Eaches sold was approximately 1.5. The abuse ratios for DXM, were lower than those for diphenhydramine and codeine containing products and somewhat higher than abuse ratio for pseudoephedrine products.

1 INTRODUCTION

This review is in response to a consult request made by the CSS for an analysis of adverse events associated with the abuse, misuse, overdose, and related deaths of single ingredient DXM as well as for comparator drugs: diphenhydramine, pseudoephedrine and codeine products that are scheduled as a C-V products under the CSA. CSS asked OSE to provide an updated analysis of drug utilization and DAWN from calendar year 2004 through 2008. This is a follow-up to the consult completed in November 12, 2009 that examined both AERS as well as DAWN data for events related to drug misuse and abuse of DXM products.

2 BACKGROUND

Dextromethorphan (DXM), a non-narcotic anti-tussive, is used for the temporary relief of cough caused by minor throat and bronchial irritation such as may occur with common cold or with inhaled irritants. DXM is most effective in the treatment of chronic, nonproductive cough. It is a common ingredient available commercially in cough mixtures that do not require a prescription.

DXM is neither a controlled substance nor a regulated chemical under the CSA. The CSA specifically excluded DXM from any of the schedules in 1970 because of a lack of significant opiate-like abuse potential. However the CSA provided that DXM could be in the future added as a controlled substance through the traditional scheduling process if warranted.

3 DRUG UTILIZATION

3.1 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis. We examined total sales volume in Eaches (bottles, packets, individual unit packages) and Extended Units (tablets, capsules, mL) sold for single-ingredient DXM containing products using the IMS Health, IMS National Sales Perspectives™ (see Appendix for full description) for calendar years 2004 through 2008.

Because these products are sold to consumers in bottles and individual unit packages, we chose Eaches as the unit of analysis for this review. Extended Units represent tablets, capsules, and

mL of product sold. Since these products are available in all three dosage forms, but are consumed in varying amounts depending on the dosage form, we chose not to use this measure as the unit of analysis.

3.2 RESULTS

3.2.1 Sale of Dextromethorphan-Containing Products

Table 1 below shows the estimated total number of single-ingredient dextromethorphan and the comparator drugs: diphenhydramine, pseudoephedrine and codeine C-V products sold in Eaches from the manufacturer to U.S. wholesale distribution channels for years 2004 through 2008.

Table 1. Estimated total number of Eaches (bottles, packets, individual unit packages) of single ingredient dextromethorphan, diphenhydramine, pseudoephedrine and codeine C-V products sold, in thousands (000), from the manufacturer to U.S. wholesale distribution channels, Years 2004-2008

	2004	2005	2006	2007	2008
dextrophethorphan	11,879.50	10,174.60	9,766.30	11,682.00	10,283.30
diphenhydramine	47,553.50	53,805.80	50,700.80	51,708.50	56,184.10
pseudoephedrine	20,037.20	19,484.80	15,023.90	15,049.10	15,061.40
codeine* (C-V products)	6,620.90	7,582.20	6,551.60	6,814.90	8,679.60

Source: IMS Health, IMS National Sales Perspectives™, Years 2004 - 2008, Extracted 11-4-09, and 3/8/10
*Includes only combination cough/cold codeine preps

4 EPIDEMIOLOGICAL ANALYSIS

4.1 DATA SOURCES USED

Drug Abuse Warning Network (DAWN)

DAWN, administered by the Substance Abuse and Mental Health Services Administration (SAMHSA), is an active public health surveillance system that examines drug related emergency room visits. DAWN monitors drug-related visits to hospital emergency departments (EDs) and provides data on patients treated in hospital emergency departments. Drug-related ED visits are found by retrospective review of medical records in a national sample of hospitals. Hospitals eligible for DAWN include non-Federal, short-term, general hospitals that operate 24-hour EDs.

Inclusion and Exclusion Criteria

National estimates of drug related ED visits for single ingredient DXM-containing products for the years 2004–2008 were obtained from SAMHSA. Estimates were also provided for the following single ingredient comparator products: diphenhydramine, pseudoephedrine as well as for codeine products that fall under the C-V level of control under the CSA. Codeine C-V products were selected because these products are already controlled under the CSA. A list of codeine C-V products can be found in the Appendix.

This analysis focuses specifically on single ingredient products containing DXM or one comparator. Combination products were excluded from this analysis due to the high number of combination products containing DXM as well as comparator products. Thus, DAWN estimates were requested specifically for single ingredient products.

DAWN Data National Estimates

There are two types of ED visits related to misuse and abuse: all misuse/abuse (AllMA) and the nonmedical use of pharmaceuticals (NMUP). AllMA and NMUP are SAMHSA defined constructs that combine various types of cases of ED visits recorded in DAWN. NMUP includes

ED visits where the patient exceeded the prescribed or recommended dose, i.e. overmedication, used drugs prescribed for another person, or substance abuse (categorized by "other"). AllMA is a more comprehensive group, it includes all the NMUP visits plus any visits where the use of an illicit drug or alcohol is noted in the ED visit record.

National estimates were not provided for all the data requested. If the relative standard error (RSE)[1] is greater than 50, national estimates are not provided by SAMHSA. As a result data were not available for codeine C-V products for the years 2004-2007.

Abuse Ratio Estimates

This analysis utilizes data obtained from the DAWN as well as data on drug utilization obtained from MS Health, IMS National Sales Perspectives™.

Since the number of ED visits may be an artifact of higher levels of drug use in general, drug utilization data were incorporated into this analysis. An abuse ratio was calculated by dividing the number of ED visits that were the result of drug abuse (AllMA or NMUP) by 10,000 "Eaches" using the IMS Health, IMS National Sales Perspectives™ database.

Abuse Ratio = AllMA ED Visits or NMUP ED Visits/10,000 "Eaches"

4.2 RESULTS

Table 2 summarizes all ED visits associated with single ingredient DXM and the comparator drugs products, diphenhydramine, pseudoephedrine, and codeine C-V products. There were approximately 3,500 ED visits associated with DXM in 2004 and that number rose to more than 3,900 in 2008. The number of ED visits for the comparator drugs diphenhydramine and pseudoephedrine were considerably higher throughout the study period. For diphenhydramine there were 27,000 ED visits in 2004 and 35,000 ED visits in 2008. ED visits associated with pseudoephedrine ranged from 5,400 visits in 2004 to almost 8,000 ED visits in 2008.The number of ED visits associated with codeine C-V products (926) was considerably lower than ED visits for DXM in 2004, but in 2008 there were 4,874 ED visits for codeine C-V products, which was higher than for DXM products.

The number of ED visits per 100,000 population for DXM, pseudoephedrine, and codeine C-V products were approximately 1 per 100,000 population, but for diphenhydramine products, it ranged from 9 ED visits per 100,000 population in 2004 to more than 11 per 100,000 population in 2008.

[1] Relative standard error is calculated by dividing the standard error of the estimate by the estimate itself, then multiplying that result by 100. Relative standard error is expressed as a percent of the estimate.

Table 2: Summary of National Estimates of ED Visits Reported in DAWN for DXM and Comparator Products and Proportion related to Misuse and Abuse, 2004-2008

DAWN: National Estimates of All ED Visits					
	2004	**2005**	**2006**	**2007**	**2008**
DXM	3,529	2,766	3,181	3,438	3,914
diphenhydramine	27,031	28,615	32,949	33,502	35,215
pseudoephedrine	5,414	6,632	8,786	10,410	7,933
codeine* C-V	926	2,505	1,201	3,613	4,874
Rates: Number of ED Visits per 100,000 Population					
DXM	1.2	0.9	1.1	1.1	1.3
diphenhydramine	9.2	9.7	11.0	11.1	11.6
pseudoephedrine	1.8	2.2	2.9	3.5	2.6
codeine* C-V	0.3	0.8	0.4	1.2	1.6

Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network
*Includes only combination cough/cold codeine preps

Table 3 displays the number of ED visits for all case types as well as for AllMA related ED visits and the proportion of ED visits that were abuse-related. The proportion of total ED visits that were abuse-related for DXM products as well as for diphenhydramine was close to 50%. However, the proportion of total ED visits that were abuse-related for pseudoephedrine and codeine C-V products was lower, close to 20%.

Table 3: Summary of National Estimates of All ED Visits Reported in DAWN for DXM and Comparator Products and Proportion related to Misuse and Abuse, 2004-2008

National Estimates of All ED Visits					
Year	**2004**	**2005**	**2006**	**2007**	**2008**
DXM	3,529	2,766	3,181	3,438	3,914
diphenhydramine	27,031	28,615	32,949	33,502	35,215
pseudoephedrine	5,414	6,632	8,786	10,410	7,933
codeine* (C-V Respiratory Agents)	926	2505	1201	3613	4874
National Estimates ALLMA ED Visits					
DXM	1,822	1,226	1,488	2,095	2,159
diphenhydramine	12,954	12,905	15,907	15,625	16,689
pseudoephedrine	2,136	1,063	1,832	2,011	1,354
codeine* (C-V Respiratory Agents)	...	...	...	...	1,085
Percent of All ED Visits that are Abuse Related (AllMA)					
DXM	51.6%	44.3%	46.8%	61.0%	55.2%
diphenhydramine	47.9%	45.1%	48.3%	46.6%	47.4%
pseudoephedrine	39.4%	16.0%	20.9%	19.3%	17.1%
codeine* (C-V Respiratory Agents)	...	...	...	...	22.3%

Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network
*Includes only combination cough/cold codeine preps

Table 4 shows the national estimates of NMUP ED visits associated with single ingredient DXM containing products as well as for the comparator drugs and their respective abuse ratios.

There were approximately 1,700 ED visits per year for DXM products in 2004 and that number remained stable through year 2008. The number of NMUP ED visits associated with diphenhydramine was around 10,000 in 2004 and around 13,000 in 2008. The number of NMUP ED visits associated with pseudoephedrine dropped from roughly 1,800 visits in 2004 to 1,100 visits in 2008. The estimates for codeine C-V products were suppressed for years 2004 to 2007. However, the estimated number of NMUP ED visits associated with codeine C-V products for year 2008 was over 800.

The numbers of Eaches sold for single ingredient DXM products was stable, approximately 12 million per year through the study period. The numbers of Eaches sold for diphenhydramine increased by almost 10 million; there were 47 million Eaches sold in 2004 and more than 56 million Eaches sold in 2008. Sales for pseudoephedrine products dropped in that same time period from 20 million in 2004 to 15 million in 2008. Sales of codeine C-V products ranged from 6.6 million Eaches in 2004 to 8.7 million Eaches in 2008.

The NMUP ratio for single ingredient DXM products was about 1.5 ED visits per 10,000 Eaches for all four years. The NMUP ratio for diphenhydramine products was about 2 ED visits per 10,000 Eaches for all four years. The NMUP ratios for pseudoephedrine was usually below 1 per 10,000 Eaches sold. The NMUP ratios for codeine C-V products could only be calculated for 2008 and it was 1 NMUP ED visits per 10,000 Eaches sold.

Table 4: National Estimates of Non-Medical Use of Pharmaceuticals (NMUP) ED Visits Reported in DAWN and Number of ED Visits per 10,000 Eaches (bottles, packets, individual unit packages) for DXM and Comparator Products, 2004-2008

DAWN: NMUP ED Visits					
Year	**2004**	**2005**	**2006**	**2007**	**2008**
DXM	1,688	1,163	1,326	1,912	1,536
diphenhydramine	10,452	10,294	12,291	12,539	13,531
pseudoephedrine	1,864	1,007	1,511	1,665	1,156
codeine* (C-V Respiratory Agents)	...	...	...	...	882
IMS National Sales Perspectives: Numbers Are In Thousands (000)s					
DXM	11,879.50	10,174.60	9,766.30	11,682.00	10,283.30
diphenhydramine	47,553.50	53,805.80	50,700.80	51,708.50	56,184.10
pseudoephedrine	20,037.20	19,484.80	15,023.90	15,049.10	15,061.40
codeine* (C-V Respiratory Agents)	6,620.90	7,582.20	6,551.60	6,814.90	8,679.60
NMUP Abuse Ratio: ED Visits per 10,000 Bottles Sold					
DXM	1.4	1.1	1.4	1.6	1.5
diphenhydramine	2.2	1.9	2.4	2.4	2.4
pseudoephedrine	0.9	0.5	1.0	1.1	0.8
codeine* (C-V Respiratory Agents)	...	...	...	...	1.0

Sources: IMS Health, IMS National Sales Perspectives™, Years 2004 - 2008, Extracted 11-4-09, and 3/8/10; and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network
*Includes only combination cough/cold codeine preps

Table 5 shows the national estimates of AllMA ED visits associated with DXM containing products. Since the AllMA category is more comprehensive than the NMUP category, all the estimates are somewhat higher.

There were about 1,800 ED visits per year studied for DXM products that were associated with AllMA in 2004. The abuse ratio for DXM products is about 1.5 ED visits per 10,000 Eaches in 2004 and 2.1 ED visits per 10,000 Eaches sold in 2008. For diphenhydramine products, the AllMA ratios were higher than for DXM, 2.7 ED visits per 10,000 Eaches in 2004 and 3.0 ED visits per 10,000 Eaches sold in 2008. The AllMA ratios for codeine C-V products could only be calculated for the year 2008 and it was 1.3 per 10,000 Eaches sold.

Table 5: National Estimates of All Misuse and Abuse Use of Pharmaceuticals (AllMA) ED Visits Reported in DAWN and Number of ED Visits per 10,000 Eaches (bottles, packets, individual unit packages) for DXM and Comparator Products, 2004-2008

DAWN: ALLMA ED Visits					
Year	**2004**	**2005**	**2006**	**2007**	**2008**
DXM	1,822	1,226	1,488	2,095	2,159
diphenhydramine	12,954	12,905	15,907	15,625	16,689
pseudoephedrine	2,136	1,063	1,832	2,011	1,354
codeine* (C-V Respiratory Agents)	...	...	...	...	1,085
IMS National Sales Perspectives: Numbers Are In Thousands (000)s					
DXM	11,879.50	10,174.60	9,766.30	11,682.00	10,283.30
diphenhydramine	47,553.50	53,805.80	50,700.80	51,708.50	56,184.10
pseudoephedrine	20,037.20	19,484.80	15,023.90	15,049.10	15,061.40
codeine* (C-V Respiratory Agents)	6,620.90	7,582.20	6,551.60	6,814.90	8,679.60
AllMA Abuse Ratio: ED Visits per 10,000 Bottles Sold					
DXM	1.5	1.2	1.5	1.8	2.1
diphenhydramine	2.7	2.4	3.1	3.0	3.0
pseudoephedrine	1.1	0.5	1.2	1.3	0.9
codeine* (C-V Respiratory Agents)	...	...	...	...	1.3

Source: IMS Health, IMS National Sales Perspectives™, Years 2004 - 2008, Extracted 11-4-09, and 3/8/10; and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network
*Includes only combination cough/cold codeine preps

5 DISCUSSION AND CONCLUSION

DAWN data suggests that the use of DXM is associated with intentional misuse for abuse purposes. However, it does not indicate that DXM products are widely abused. There were close to 2,000 ED visits per year that were associated with single ingredient DXM products. Approximately half of the ED visits attributed to the use of DXM were related to abuse and misuse of the product. The number of AllMA ED visits per 10,000 Eaches sold was approximately 1.5. The abuse ratios, however, were higher for diphenhydramine containing products and somewhat lower for pseudoephedrine products.

It is important to note that DAWN data provides data on misuse and abuse of drug products that result in an emergency room visit. Therefore, if the abuse is not severe enough to result in an ED visit or if the event results in a death, these events will not be collect in DAWN data.

APPENDIX

1. DRUG UTILIZATION DATABASE DESCRIPTION

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

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

2. LIST OF CODEINE C-V PRODUCTS

List of Products that are Schedule C-V Codeine Phosphate Products	
PEDIACOF PEDIATRIC COUGH SYRUP	GUAIFENESIN DM SYRUP
POLY HISTINE CS SYRUP	PROMETHAZINE HCL AND CODEINE SYRUP
PROMETHAZINE HCL AND CODEINE PHOSPHATE SYRUP	GUIATUSS AS SYRUP
IOFEN C NF LIQUID SUGAR FREE ALCOHOL FREE	GUAIFENESIN AND CODEINE PHOSPHATE ORAL SOLUTION
IOPHEN C NR LIQUID	ENDAL CD SYRUP
CHERATUSSIN AC LIQUID EXPECTORANT COUGH SUPPRESSANT SUGAR FREE	CHERATUSSIN AC EXPECTORANT COUGH SUPPRESSANT SUGAR FREE LIQUID
GUAIFENESIN AND CODEINE LIQUID	PROMETHAZINE WITH CODEINE SYRUP
IOPHEN C NR LIQUID	ACETAMINOPHEN AND CODEINE PHOSPHATE SOLUTION ORAL
PHENYLHISTINE DH LIQUID	PROMETHAZINE VC CODEINE COUGH SYRUP
PROMETHAZINE WITH CODEINE SYRUP	NUCOFED SYRUP
PROMETHAZINE VC WITH CODEINE SYRUP	NUCOFED PEDIATRIC EXPECTORANT SYRUP
PEDIACOF SYRUP PEDIATRIC COUGH	NUCOFED EXPECTORANT LIQUID
PENTAZINE SYRUP WITH CODEINE	CODEINE WASTE SYRUP
PENTAZINE VC SYRUP WITH CODEINE	GENCOFED SYRUP FORMULA
C TUSSIN LIQUID	GENCOFED EXPECTORANT FORMULA SYRUP
ANTITUSS AC SYRUP	GENCOFED PEDIATRIC EXPECTORANT FORMULA
NUCOTUSS PEDIATRIC EXPECTORANT SYRUP	GANI TUSS NR LIQUID
NUCOTUSS EXPECTORANT SYRUP	PROMETH WITH CODEINE COUGH SYRUP
PROMETHAZINE WITH CODEINE SYRUP COUGH	GUIATUSS WITH CODEINE SYRUP
PROMETH VC WITH CODEINE COUGH SYRUP	PROMETHAZINE WITH CODEINE SYRUP
SUDATUSS 2 SYRUP	PROMETHAZINE VC WITH CODEINE SYRUP
SUDATUSS SF SYRUP	DIHISTINE EXPECTORANT
ACETAMINOPHEN AND CODEINE PHOSPHATE ORAL SOLUTION USP	PROMETHAZINE WITH CODEINE SYRUP
BROMANYL COUGH SYRUP	CHLORPHENIRAMINE CODEINE PHOSPHATE AND PSEUDOEPHEDRINE LIQUID
CHERATUSSIN AC LIQUID EXPECTORANT COUGH SUPPRESSANT SUGAR FREE	GUIAFENESIN WITH CODEINE SYRUP
CHERATUSSIN DAC SYRUP	PROMETHAZINE HCL WITH CODEINE COUGH SYRUP
CODAFED LIQUID PEDIATRIC EXPECTORANT	MYTUSSIN DAC
CODAFED LIQUID EXPECTORANT	TUSSI ORGANIDIN S NR LIQUID
GUAIFEN C LIQUID	PROMETHAZINE VC SYRUP WITH CODEINE
IOPHEN C NR LIQUID	GUIATUSS AC SYRUP
PHENYLHISTINE DH LIQUID	DIHISTINE EXPECTORANT LIQUID
POLY CS SYRUP	PHENERGAN WITH CODEINE SYRUP
PROMETHAZINE WITH CODEINE SYRUP COUGH	PROMETHAZINE WITH CODEINE SYRUP
PROMETHAZINE VC WITH CODEINE COUGH SYRUP	PROMETH VC WITH CODEINE SYRUP
PROMETHAZINE WITH CODEINE SYRUP	GUAIFENESIN AC SYRUP

List of Products that are Schedule C-V Codeine Phosphate Products

PROMETHAZINE VC WITH CODEINE SYRUP

QUINDAL EXPECTORANT LIQUID

QUINDAL EXPECTORANT LIQUID

TRIPROLIDINE C LIQUID

TUSSO C SYRUP

PROMETHAZINE WITH CODEINE SYRUP

PROMETHAZINE VC WITH CODEINE SYRUP

PROMETHAZINE SYRUP COUGH WITH DEXTROMETHORPHAN

UNI MULTIHIST CS SYRUP SUGAR FREE

PROMETHAZINE VC WITH CODEINE COUGH SYRUP

PROMETHAZINE WITH CODEINE COUGH SYRUP

ROBAFEN AC COUGH SYRUP

BROMODIPHENHYDRAMINE HYDROCHLORIDE AND CODEINE PHOSPHATE COUGH SYRUP

DIAMINE DC COUGH SYRUP

PROMETHAZINE WITH CODEINE SYRUP COUGH

PROMETHAZINE VC SYRUP COUGH WITH CODEINE

APRODINE WITH CODEINE LIQUID

ROBAFEN AC COUGH SYRUP

IOPHEN LIQUID

PPA BROMPH CODEINE SYRUP SUGAR FREE

ACETAMINOPHEN WITH CODEINE PHOSPHATE ORAL SOLUTION USP

TRICODENE SYRUP #1 WITH CODEINE CV

TRIPROLIDINE PSEUDOEPHED WITH CODEINE COUGH SYRUP

PROMETH WITH CODEINE COUGH SYRUP

DEMI COF COUGH SYRUP PEDIATRIC

CODEINE PROMETH SYRUP

SUTTAR 2 LIQUID

BIOTUSSIN AC V SYRUP

GANI TUSS NR LIQUID

TRIPROLIDINE HYDROCHLORIDE PSEUDOEPHEDRINE HYDROCHLORIDE AND CODEINE PHOSPHATE SYRUP COUGH

BROMODIPHENHYDRAMINE HYDROCHLORIDE AND CODEINE PHOSPHATE COUGH SYRUP

PROMETHAZINE WITH CODEINE SYRUP COUGH

PROMETHAZINE VC WITH CODEINE SYRUP COUGH

DIABETIC TUSSIN C

GUAIFENESIN NR LIQUID WITH CODEINE

PROMETHAZINE WITH CODEINE CV SYRUP

PROMETHAZINE VC WITH CODEINE SYRUP

GUAIFENESIN AND CODEINE CV SYRUP

GUAIFENESIN AND CODEINE PHOSPHATE ORAL SOLUTION

GUAITUSSIN AC LIQUID

GUAITUSSIN DAC LIQUID

TUSSI ORGANIDIN S NR LIQUID

CHERATUSSIN AC COUGH SUPPRESSANT

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

Date: August 11, 2010

To: Michael Klein, Ph.D., Director
Controlled Substance Staff

Thru: Mary Willy, Ph.D.
Deputy Director, Division of Risk Management (DRISK)
Office of Surveillance and Epidemiology (OSE)

From Dextromethorphan Health Education Review Team
Marcia Britt, Ph.D., Health Education Reviewer
Kate Heinrich, M.A., Health Education Reviewer

Subject: Review of Consumer Healthcare Products Association (CHPA) website

Drug Name: Dextromethorphan

Application Number: ANDA 40-649, 40-027, 89-681, 88-864, 88-811, 88-762,
NDA 21-620, 11-265, 18-658

OSE RCM Number: 2010-1292

INTRODUCTION

This review of the Consumer Healthcare Products Association (CHPA) website provides the Controlled Substance Staff with information about the content of the dextromethorphan-related website information and recommendations for improving the website as an educational tool. The Food and Drug Administration, Division of Risk Management (DRISK), reviewed the content and format of the CHPA website, specifically the Dextromethorphan and Stopping Cough Medicine Abuse Quick Link.

I. BACKGROUND

The Consumer Healthcare Products Association (CHPA) is a member-based association representing the leading manufacturers and distributors of nonprescription, over-the-counter (OTC) medicines and nutritional supplements. CHPA developed a website www.chpa-info.org, Dextromethorphan and Stopping Cough Medicine Abuse, as an awareness campaign to alert parents and educators about the potential misuse and intentional abuse of over-the-counter (OTC) cough and cold medicines that contain dextromethorphan by teenagers and young adults. Dextromethorphan, when taken in large quantities, creates euphoria and has been used to 'get high'. The CHPA website provides a designated link to the Dextromethorphan and Stopping Cough Medicine Abuse website.

The Division of Risk Management reviewed the CHPA website, Dextromethorphan and Stopping Cough Medicine Abuse, to determine the adequacy of the information and format of the website.

II. RESULTS OF REVIEW OF CHPA WEBSITE

The review of the website identified the following concerns:

Overall Issues with Single Source Dissemination

- CHPA's use of only a single source, the CHPA website, to convey misuse and abuse issues related to dextromethorphan reduces the likelihood of reaching certain audience(s).
  - Persons who lack of access to the internet
  - Persons who are not aware that the website exists due to limited distribution or 'marketing' of the website:
    - A parent or educator would have to seek out information about cough medicine abuse and then hope that they stumble upon the website in their search for information.

Problems with the Website

- CHPA Home page:
  - The cough medicine abuse information is not easy to locate on the CHPA homepage website. The link, "Dextromethorphan and stopping cough medicine abuse," is provided under the "Quick Links" section on the bottom right of homepage above "CHPA's Executive Newsletter." The link should be more prominent on the website to stand out.

- Parents looking for information won't necessarily know the term "Dextromethorphan." Starting the link with that term could be confusing and lead it to be overlooked.

- Dextromethorphan and Stopping Cough Medicine Abuse Overview page:
  - This page is very busy and has lots of information. One has to read through a lot of information, scroll down, and click on various links to find the information one may be seeking. One could easily be sent through various links and get "lost" in other resources, become frustrated, and give up searching and/or not find the way back to this page. For example:
    - Once on the Dextromethorphan and Stopping Cough Medicine Abuse Overview web page, the current layout does not have a clearly defined section for dextromethorphan educational material and information. As this site is currently designed, the dextromethorphan material is sporadic and is not placed in a designated location.
    - The "FAQ's About Dextromethorphan" link is on the left hand side of the page and mixed in with all other links from the CHPA website. Although it is shaded differently, it may not be obvious to all users looking for this information.
    - There are a number of different links targeting different audiences on the dextromethorphan page. It may be difficult to find the correct link for a parent or educator, or once sent to a new page, one may not find his or her way back to the dextromethorphan page.

- Target Audience:
  - The website appears to target only parents and educators. The target audience needs to be expanded to reach a broader audience such as:
    - Tweens (ages 10-12)
    - Teenagers (ages 13-17)
    - Young adults (ages 18-24)
    - Adults including: Parents, School teachers, School administrators (including counselors)

    Although we agree with targeting parents and educators, research has shown that as teenagers get older, peer influence becomes a greater influence on adolescent substance use than parental influence.[1,2]

III. RECOMMENDATIONS

After review of the CHPA dextromethorphan website, DRISK recommends the following:

1. Include multifaceted educational resources targeted to a variety of audiences including tweens, teens and young adults. Consider links and educational materials from the webpage that contain messages and

[1] Sawyer, T.M. & Stevenson, J.F. (2008). Perceived parental and peer disapproval toward substances: Influences on adolescent decision-making. *The Journal of Primary Prevention, 29*, 465-477.

[2] Pandina, R.J., Johnson V.L., & White H.R. (2010). Peer influences on substance use during adolescence and emerging adulthood. In L.M. Scheier (Ed.), *Handbook of drug use etiology*, (1st ed., pp. 383-402). Washington, DC: American Psychological Association

materials appropriately targeting each audience, as they are distinctly different.

2. Create a webpage designated specifically for dextromethorphan educational material. The educational material should be easily identified and accessible by the end user.

IV. SUMMMARY

While CHPA created a series of dextromethorphan weblinks to engage parents and educators about the risks associated with dextromethorphan, the Dextromethorphan and Stopping Cough Medicine Abuse weblink does not display safety information adequately; placement of educational material on the webpage is not intuitive and difficult to locate and then access by the end user.

The CHPA dextromethorphan campaign for stopping cough medicine abuse as a whole does not target all the audiences affected by this public health issue. In particular, the website does not provide health education and behavioral information specifically for tweens, teenagers and young adults.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-11265	ORIG-1	ANI PHARMACEUTICALS INC	PHENERGAN W/ DEXTROMETHORPHAN
NDA-18658	ORIG-1	RECKITT BENCKISER	DELSYM
NDA-21620	ORIG-1	RECKITT BENCKISER INC	MUCINEX DM (GUAIFENESIN/DEXTROMETHORPHAN

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

/s/

MARY J DEMPSEY
08/12/2010

MARY E WILLY
08/12/2010
I concur