FDA Briefing Document

Drug Safety and Risk Management Advisory Committee (DSaRM)
Meeting – October 29-30, 2012

DISCLAIMER

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Draft Discussion Points for Advisory Committee Meeting

1. (DISCUSSION) What do the pharmacology data and the epidemiology data suggest about the potential for abuse of hydrocodone combination products compared with drugs that are currently in schedule II?

2. (DISCUSSION) What impact would rescheduling of hydrocodone combination products from schedule III to II have on the following:
Prescribing patterns for opioids, including hydrocodone combination products? Delivery of healthcare in the US, including impacts on drug distribution, manufacturing, prescription and dispensing by pharmacies? Availability of hydrocodone combination products for patients with appropriate needs for them as well as by individuals seeking to abuse opioids? Abuse and misuse of opioids, especially hydrocodone combination products?

3. (DISCUSSION) Are there other activities that could reduce abuse and misuse of these products?

4. (VOTE) Based on the background materials, presentations and the discussion above, do you recommend that hydrocodone combination products be rescheduled from schedule III to schedule II of the CSA? Please explain the basis for your vote.

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 2, 2012

To: Douglas Throckmorton, M.D., Deputy Director
Center for Drug Evaluation and Research

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

From: Silvia Calderon, Ph.D., Team Leader Pharmacology
Controlled Substance Staff

Subject: Summary Review of the Controlled Substance Staff (CSS) Assessment of the Abuse of Hydrocodone Combination Products.

This memorandum summarizes findings of the re-evaluation of drug abuse-related data for hydrocodone combination products. This re-evaluation was conducted in response to the Drug Enforcement Administration's (DEA) request submitted, to the Center for Drug Evaluation and Research (CDER) on February 13, 2009.

I. BACKGROUND

Hydrocodone drug substance is listed in Schedule II of the Controlled Substances Act (CSA). Hydrocodone combination products, containing specified amount of hydrocodone and formulated with specified amounts of an isoquinoline alkaloid of opium, or one or more therapeutically active non-narcotic ingredients, are in Schedule III of the CSA, unless exempted or listed in another schedule. These combination products include marketed and approved analgesic and cough suppressant products. Although not currently available on the market, any product containing single entity hydrocodone, or combinations of hydrocodone and other substances outside the range of specified doses would be listed in Schedule II. Specifically, Schedule III controls apply to hydrocodone combination products containing no more than 300 milligrams per 100 milliliters or not more than 15 milligrams of hydrocodone base per dosage unit, with one or more active non-narcotic ingredients in recognized therapeutic amounts.

In 1999, the DEA received a Citizen Petition requesting the re-scheduling of hydrocodone combination products to Schedule II of the CSA.[1] In response to the petition, in 2004, DEA

[1] In this memorandum, the potential rescheduling of hydrocodone combination products from Schedule III to Schedule II of CSA is referred to as the "up-scheduling" of hydrocodone combination products.

requested that the Department of Health and Human Services (HHS) provide a scientific and medical evaluation of the available information and a scheduling recommendation for hydrocodone combination products (See Attachments).

Upon receipt of the DEA request, in 2004, HHS (FDA/CDER) began to collect information to respond to the petition. On March 2008, the Assistant Secretary for Health (ASH/HHS) forwarded to the Deputy Administrator of DEA its scientific and medical evaluation, entitled *Basis for the Recommendation to Maintain Hydrocodone Combination Products in Schedule III of the Controlled Substances Act*. This recommendation relied upon the assessments of FDA (Office of the Commissioner/CDER/CSS) and the concurrence of the National Institute on Drug Abuse/National Institutes of Health (NIDA/NIH).[2]

In my view, one of the main findings supporting this recommendation was that hydrocodone combination products have a less potential for abuse than the drugs or other substances in Schedule II (See Attachments). The lower abuse potential determination was based upon consideration of the following data:

1. *The abuse-related pharmacology of the combination products*. The addition of a non-narcotic active ingredient lowered the potential for abuse of hydrocodone combination products (Schedule III) compared to hydrocodone substance (Schedule II) in two ways. The addition of a non-narcotic active component reduces the amounts of hydrocodone needed to reach the desired therapeutic effect and limits in this way the intake of hydrocodone to lower doses that might not be perceived by patients as reinforcing and pleasant. Second, the non-narcotic active component may cause toxic, dysphoric and unpleasant effects when high doses of these products are ingested for abuse and misuse purposes, and these effects mitigate any desired effects.

2. *Epidemiological analysis of data on levels of abuse of the hydrocodone combination products relative to similar opioid containing drug products.* To evaluate the relative levels of abuse of a substance FDA/CDER/NIDA relies upon comparisons of "abuse ratios" among substances with similar pharmacology and medical use. In calculating these ratios, the numerator is an abuse-related event, such as Drug Abuse Warning Network (DAWN) Emergency Department (ED) visits, and the denominator is a measure of the availability of the drug. Comparisons of "abuse ratios" between hydrocodone and other similar opioids showed that the abuse of hydrocodone combination products was lower than that of other Schedule II opioid containing products, and was similar to that of other Schedule III opioid containing products.

In response to the 2008 HHS recommendation, DEA collected and re-analyzed new data regarding the abuse and diversion of hydrocodone combination products, and in 2009 submitted the request to CDER to reconsider the up-scheduling of all hydrocodone combination products (See Attachments). Within CDER, the Division of Analgesia, Anesthesia, and Addiction

[2] Administrative responsibilities for evaluating a substance for control under the CSA are performed for HHS by FDA, with the concurrence of the National Institute on Drug Abuse (NIDA) (Memorandum of Understanding, March 8, 1985, 50 FR 9518-20).

Products (DAAAP) addressed the role of hydrocodone combination products in the treatment of pain. The Division of Epidemiology (DEPI), Office of Surveillance and Epidemiology (OSE) (DEPI/OSE) addressed aspects related to drug utilization (number of prescriptions, prescribers, days of therapy and diagnoses associated) as well as it conducted the re-evaluation of the epidemiological data available (See Attachments), and CSS addressed the overall abuse potential assessment. A summary of the key findings of the FDA/CDER re-analysis of the updated data collected by DEA, as well as my assessment and conclusions are provided in the following sections of this memo.

II. FDA/CDER/CSS'S RE-ANALYSIS OF THE DATA SUBMITTED BY DEA IN SUPPORT OF UP-SCHEDULING OF HYDROCODONE COMBINATION PRODUCTS.

The following analysis reviews DEA's re-analysis and main arguments in support of the up-scheduling of hydrocodone combination products. In the following sections I address:

1. Availability, 2. Abuse Liability Studies and Abuse Potential, and 3. Actual Indicators of Abuse (Epidemiological Data).

In Section **4. Potential Consequences of Up-scheduling Hydrocodone Combination Products**, I offer an overview of the impact of the up-scheduling on manufacturers, prescribers, dispensers and patients.

1. Availability

Based on drug utilization data provided by DEPI/OSE, I agree with the DEA that hydrocodone combination products and in particular hydrocodone/acetaminophen containing products are widely prescribed. Recognizing the prime role of these combination products in the management of pain, as pointed out by DAAAP in their review, I conclude that the large number of prescriptions annually dispensed for hydrocodone combination captures the medical use of these products for management of pain. The widespread use of these products reflects that these products are indicated for the management of moderate to moderately severe pain and are appropriate for use in a wide range of painful conditions including acute postoperative pain, chronic non-cancer pain including musculoskeletal pain, and cancer pain. In addition, the selection of hydrocodone/acetaminophen products by prescribers, rather than Schedule II products, may also reflect the lower burden for prescribers and patients under Schedule III compared to Schedule II. In the following sections I have summarized the main points on the medical use and drug utilization data from the DAAAP and DEPI/OSE reviews, and I have reproduced **Tables** and **Figures** on drug utilization from the DEPI/OSE review (See Attachments for DAAAP's and DEPI/OSE's reviews)

1.1. Medical Use

Hydrocodone/acetaminophen combination products are an important option for the treatment of pain. Hydrocodone/acetaminophen combination products are part of the Step 2 therapeutic

option on the World Health Organization (WHO) Analgesic Ladder.[3] The associated WHO guidance for the treatment of cancer pain states that the use of the hydrocodone combination products is recommended prior to the initiation of therapy with a more potent opioid indicated for the treatment of moderate to severe pain (World Health Organization, 1986.) Opioid analgesic products are typically prescribed after non-opioid analgesics are no longer adequate to manage pain or are no longer tolerated due to adverse effects. Non-opioid analgesics, such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), constitute Step 1 therapeutic option on the WHO Analgesic Ladder. Initial opioid analgesics prescribed include tramadol and the opioid combination products consisting of hydrocodone and acetaminophen or oxycodone and acetaminophen. Some patients may not be candidates for the use of NSAIDs due to the risk for toxicity involving the gastrointestinal, cardiovascular, renal, and hepatic systems and may need to rely on opioid analgesics earlier in the course of their pain management.

The presence of the non-narcotic analgesic in hydrocodone and other opioid combination products limits the safe maximum dose. When patients require dose escalation that exceeds these limits, single-entity opioids listed under Schedule II such as morphine, oxycodone, hydromorphone, and fentanyl are the next step (Step 3).

Data available in the literature demonstrate that hydrocodone/acetaminophen combination products provide better pain relief than the same doses of hydrocodone or acetaminophen alone. Additional reasons for the use of hydrocodone and other opioid combination products include fewer adverse reactions as a result of the lower doses of the individual components in the combination dosage unit, and improved patient compliance relative to the use of the individual components separately. (Beaver, 1984, Raffa *et al*. 2001 and 2003, Phero *et al*. 2002).[4]

The use of single entity opioids (Step 3) such as morphine (Schedule II), oxycodone (Schedule II), hydromorphone (Schedule II) and fentanyl (Schedule II) is indicated when the combination products containing lower doses of opioids have failed.

Other opioid analgesic combination products currently on the market include oxycodone in combination with acetaminophen or aspirin (Schedule II), codeine in combination with acetaminophen or in combination with aspirin, butalbital and caffeine, or in combination with carisoprodol and aspirin (Schedule III), and tramadol in combination with acetaminophen.

Several products containing hydrocodone in combination with acetaminophen, aspirin, ibuprofen, and homatropine are currently marketed as analgesics for pain relief and as cough suppressants. Available marketed strengths range from 2.5 mg to 10 mg of hydrocodone bitartrate salt. Currently marketed hydrocodone combination products are mostly generic products, and include analgesics such as Vicodin, Vicoprofen, Lortab, Lorcet, Norco, Co-Gesic,

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[3] WHO's pain ladder. http://www.who.int/cancer/palliative/painladder/en/ (Last accessed October 1, 2012)

[4] Beaver, W.T., **1984**. Combination Analgesics. Am. J. Med. 77, 38-53.
Phero, J.C., Becker, D., 2002. Rational use of analgesic combinations. Dent. Clin. North Am. 46, 691- 705.
Raffa, R. B., **2001**. Pharmacology of oral combination analgesics: rational therapy for pain. J. Clin. Pharm. Ther. 26, 257-264.
Raffa, R.B., Clark-Vetri, R., Tallarida, R.J., Wertheimer, A.I., **2003**. Combination strategies for pain management. Expert Opin. Pharmacother. 4, 1697-1708.

Hydrocet, Anexsia, Azdone, Zydone, and cough suppressants such as Hycodan, Mycodone, Tussionex Pennkinetic, Tussigon (See Attachment).

The rationale for combination analgesic products, such as hydrocodone with acetaminophen, is to provide improved analgesia due to additive or synergistic analgesia of the combination. In this way, each individual component in the combination is used at lower doses than those required at the individual basis, reducing the frequency or severity of adverse drug reactions.

1.2. Drug use information

To examine the problem of abuse related to hydrocodone combination products, DEPI/OSE first conducted a careful examination of the use of these products, and tried to compare aspects of the use of these products to other opioids for which abuse is also known to be a problem. This examination includes sales data, data on prescription/patient volume of use, prescribers specialty, duration of therapy, and indication for use, as summarized in the following subsections.

1.2.1. Sales Data

The use of combination hydrocodone-containing products for analgesia in the U.S. is widespread and continues to grow every year.

An examination of sales data from manufacturers to all channels of distribution (retail, hospital, etc) from 2007 through 2011 shows that sales of combination hydrocodone-containing analgesics far exceed sales of other selected opioid analgesics (**Figure 1**).

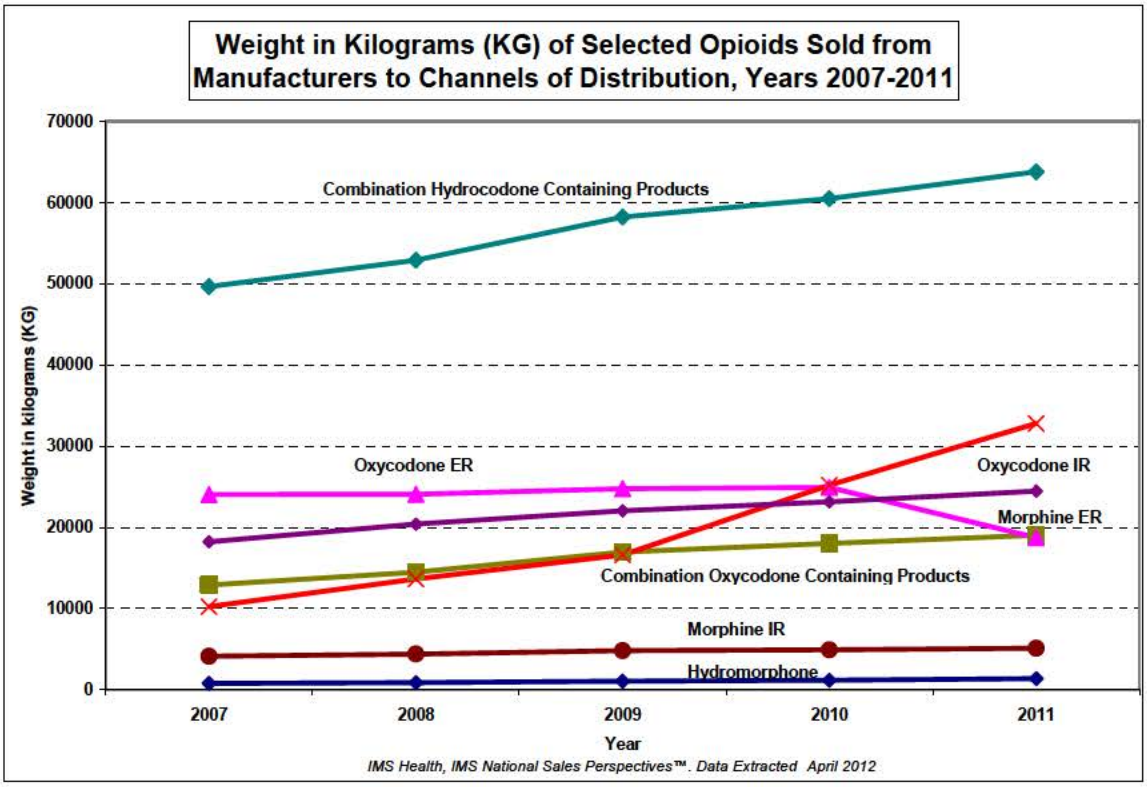

Figure 1 – Weight in Kilograms (KG) of Selected Opioid Analgesics Sold from Manufacturers to All Channels of Distribution, Years 2007-2011. (Reproduced from the DEPI/OSE Drug Utilization Review)

This increasing trend is not the case, however, for combination hydrocodone-containing products used as antitussives; the number of tablets/capsules/milliliters sold from manufacturers to all channels of distribution has declined in 2011 to less than half the volume sold in 2007 (**Figure 2**).

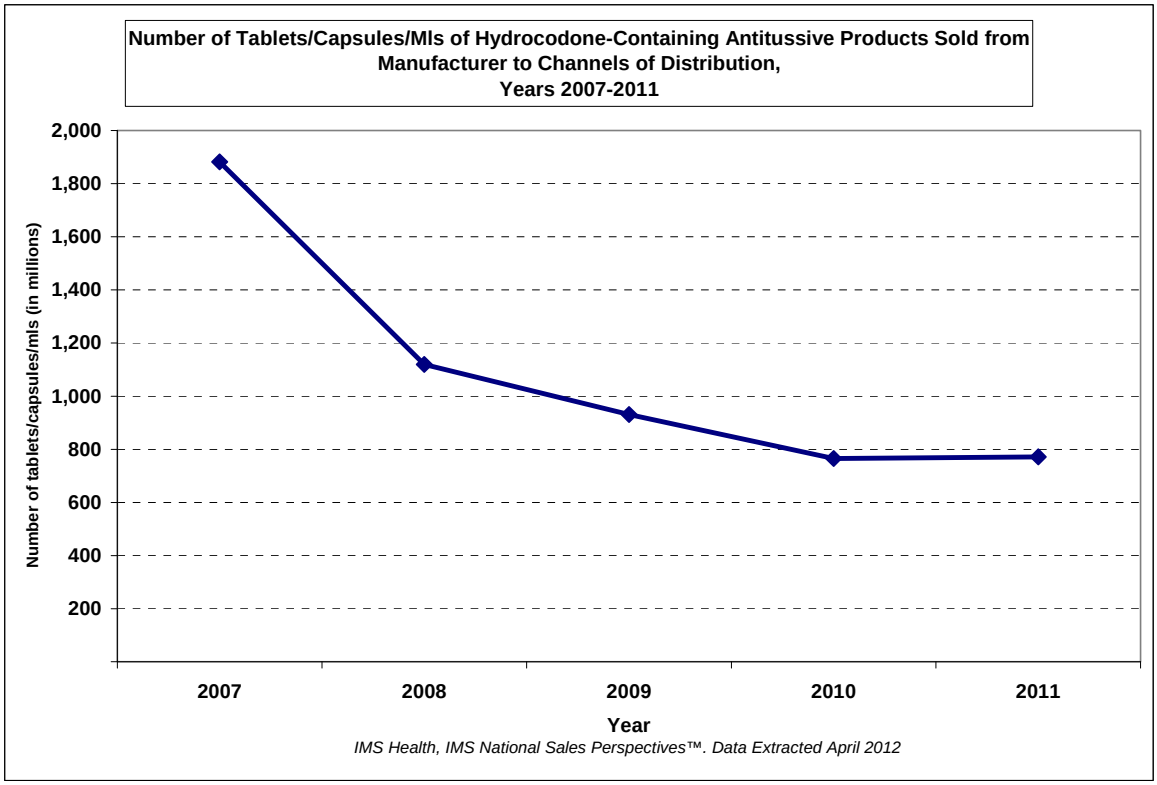

Figure 2- Number of Tablets/Capsules/MLs of Hydrocodone-Containing Antitussive Products Sold from Manufacturer to All Channels of Distribution, Years 2007-2011 (Reproduced from the DEPI/OSE Drug Utilization Review)

Given the smaller sales volume of combination hydrocodone-containing antitussives, and the lesser degree of abuse believed to be associated with these products (to be discussed later), the DEPI/OSE analysis focused on the combination hydrocodone-containing analgesics.

1.2.2. Prescription/patient volume of use

When examining patient-level use of opioid analgesic products, similar trends to the sales data are seen. The numbers of prescriptions for combination hydrocodone-containing analgesics dispensed from outpatient retail pharmacies and the numbers of patients receiving those prescriptions exceed the same measures for other selected opioid analgesics by at least 3-fold

(**Table 1, Figure 3**). Approximately 131 million prescriptions for combination hydrocodone-containing analgesics were dispensed in 2011 to approximately 47 million patients. In stark contrast, a decreasing volume of prescriptions was seen for combination hydrocodone-containing antitussives over the same time period.

Table 1: Nationally Estimated Number of Combination Hydrocodone-Containing Analgesics and Comparators (Oxycodone ER/IR, Combination Oxycodone Containing Analgesics, Morphine ER/IR, and Hydromorphone) Prescriptions Dispensed Through U.S Outpatient Retail Pharmacies, Year 2007-2011. (Reproduced from the DEPI/OSE Drug Utilization Review)

Nationally Estimated Number of Combination Hydrocodone-Containing and Comparators (Oxycodone ER/IR, Combination oxycodone-containing, Morphine ER/IR, and Hydromorphone) Prescriptions Dispensed Through U.S. Outpatient Retail Pharmacies, Years 2007-2011

	2007		2008		2009		2010		2011	
	TRx	Share %	TRx	Share %	TRx	Share %	TRx	Share %	TRx	Share %
Total Market	171,193,887	100.0%	180,024,122	100.0%	181,834,902	100.0%	189,517,906	100.0%	198,092,751	100.0%
Hydrocodone Analgesic Products	120,558,352	70.4%	124,638,107	69.2%	123,785,684	68.1%	125,749,235	66.4%	130,704,029	66.0%
Hydrocodone/Acetaminophen	118,074,137	97.9%	122,260,964	98.1%	121,575,144	98.2%	123,556,210	98.3%	128,546,058	98.3%
Hydrocodone/Ibuprofen	2,484,184	2.1%	2,377,134	1.9%	2,210,530	1.8%	2,193,014	1.7%	2,157,965	1.7%
Hydrocodone/Aspirin	31	0.0%	9	0.0%	10	0.0%	11	0.0%	6	0.0%
Total Oxycodone	43,405,133	25.4%	47,225,509	26.2%	49,419,388	27.2%	54,365,207	28.7%	56,983,248	28.8%
Oxycodone Combination	28,803,782	66.4%	30,805,888	65.2%	32,239,395	65.2%	33,704,239	62.0%	34,653,743	60.8%
Oxycodone/Acetaminophen	28,545,736	99.1%	30,596,686	99.3%	32,074,676	99.5%	33,569,445	99.6%	34,545,056	99.7%
Oxycodone/Aspirin	206,142	0.7%	179,246	0.6%	144,547	0.4%	120,401	0.4%	99,233	0.3%
Oxycodone/Ibuprofen	51,904	0.2%	29,956	0.1%	20,172	0.1%	14,393	0.0%	9,454	0.0%
Oxycodone Single Ingredient	14,601,351	33.6%	16,419,621	34.8%	17,179,993	34.8%	20,660,968	38.0%	22,329,505	39.2%
Oxycodone Immediate Release	6,304,442	43.2%	8,093,643	49.3%	9,134,757	53.1%	13,190,814	63.7%	16,591,561	74.3%
Oxycodone Extended Release	8,296,909	56.8%	8,325,977	50.7%	8,045,237	46.8%	7,470,153	36.2%	5,737,943	25.7%
Morphine Sulfate	5,581,911	3.3%	6,299,627	3.5%	6,463,446	3.6%	6,981,624	3.7%	7,635,623	3.9%
Morphine ER	4,236,471	75.9%	4,822,350	76.5%	5,104,791	79.0%	5,619,457	80.5%	6,053,915	79.3%
Morphine IR	1,345,440	24.1%	1,477,276	23.5%	1,358,655	21.0%	1,362,166	19.5%	1,581,708	20.7%
Hydromorphone	1,618,707	0.9%	1,833,332	1.0%	2,135,612	1.2%	2,387,752	1.3%	2,735,846	1.4%

Source IMS Vector One® National (VONA) extracted 09/ 2012 Source Files VONA_2012-2002_Hydrocodone _oxycodone _morphine _hydromorphone_09-20-12(1).xls VONA_2012-1613_Oxycodone_forms_09-20-12(1).xls VONA_2012-1613_Morphine_IR_and_ER_09-20-12(1).xls

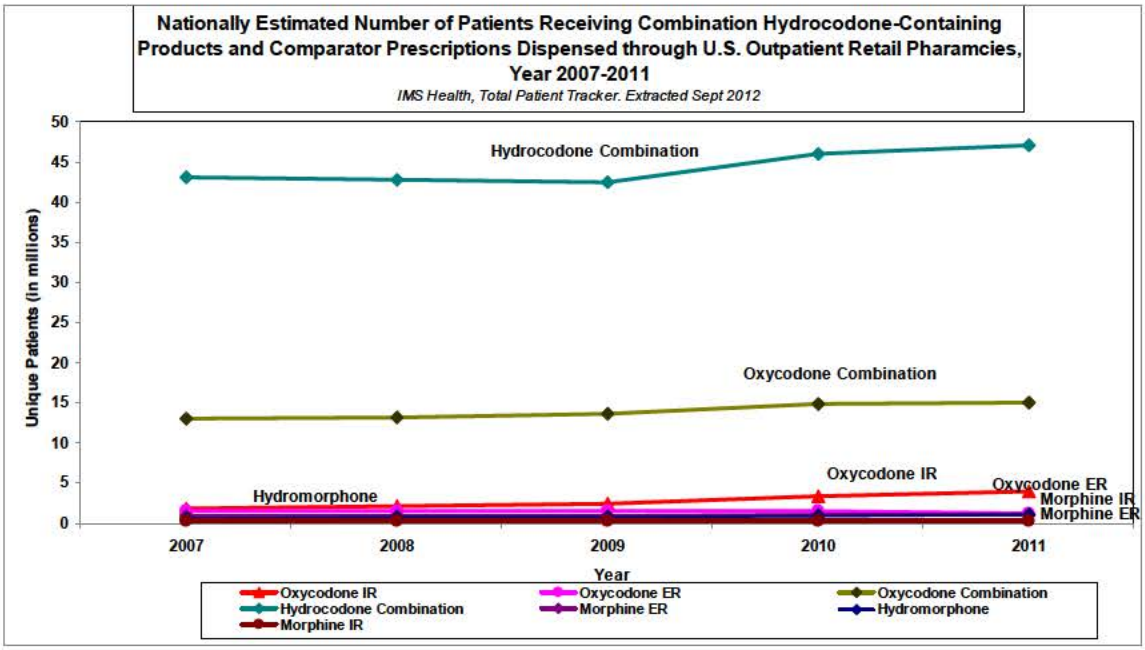

Figure 3 - Nationally Estimated Number of Patients Receiving Combination Hydrocodone-Containing Analgesics and Comparator Prescriptions Dispensed Through U.S. Outpatient Retail Pharmacies, Year 2007-2011 (Reproduced from the DEPI/OSE Drug Utilization Review)

Because the volume of prescribing and use of combination hydrocodone-containing analgesics far exceeds that of other selected opioid analgesics, DEPI/OSE attempted to examine other aspects of use to see whether there were other opioid analgesics with a similar use profile. In their review, DEPI/OSE included the following opioid-containing analgesics: combination oxycodone-containing analgesics, single-ingredient oxycodone analgesics (both immediate release [IR] and extended release [ER]), morphine products (both IR and ER) and hydromorphone products. Identifying such products represents an important step in ultimately assessing and comparing the risk of abuse associated with combination hydrocodone-containing analgesics to that associated with other products.

1.2.3. Prescriber specialty

Approximately 40% of combination hydrocodone-containing analgesics dispensed were written by general practitioners/family medicine/osteopaths and internal medicine specialists (**Table 2**).

This finding is consistent with that of other selected analgesics where this value ranges between 30% and 45%. In contrast to the other analgesics, however, 10% of combination hydrocodone-containing analgesic prescriptions dispensed were prescribed by dentists; only a small proportion of prescriptions dispensed for other selected opioids were prescribed by dentists. The number of prescriptions prescribed by anesthesiologists was relatively lower for combination hydrocodone-containing analgesics (3%) and combination oxycodone-containing analgesics (4%), as compared to other opioid analgesics: oxycodone ER (10%), oxycodone IR (9%), morphine ER (15%), morphine IR (12%), and hydromorphone (5%). In contrast, the number of dispensed prescriptions prescribed by orthopedic surgeons was relatively higher for combination hydrocodone-containing analgesics (8%) and combination oxycodone-containing analgesics (9%) as compared to the other opioid analgesics examined (<1%-5%).

Table 2: Number of Prescriptions Dispensed for Selected Opioids by Top Prescribing Specialties Through U.S. Outpatient Retail Pharmacies, Years 2007-2011 Cumulative. (Reproduced from the DEPI/OSE Drug Utilization Review)

Number of Prescriptions Dispensed for Selected Opioids by Top Prescribing Specialties Through U.S. Outpatient Retail Pharmacies, Years 2007-2011 cumulative														
	Hydrocodone Combination		Oxycodone Combination		Oxycodone IR		Oxycodone ER		Morphine IR		Morphine ER		Hydromorphone	
	TRx	Share %	TRx	Share %	TRx	Share %	TRx	Share %	TRx	Share %	TRx	Share %	TRx	Share %
General Practice/Family Practice/Osteopathy	160,181,555	25.6%	29,961,318	18.7%	12,436,964	23.3%	10,133,854	26.8%	1,790,752	25.1%	6,374,048	24.7%	1,829,683	17.3%
Internal Medicine	87,793,125	14.0%	20,013,405	12.5%	7,911,481	14.8%	6,399,322	16.9%	1,268,562	17.8%	3,860,351	14.9%	1,552,896	14.7%
Orthopedic Surgery	51,929,989	8.3%	14,248,303	8.9%	2,352,884	4.4%	1,534,447	4.1%	49,483	0.7%	312,570	1.2%	546,514	5.2%
Unspecified	35,074,830	5.6%	9,389,016	5.9%	4,344,635	8.1%	2,332,718	6.2%	516,725	7.3%	1,864,053	7.2%	720,932	6.8%
Physician Assistant	24,076,466	3.8%	8,007,884	5.0%	2,617,768	4.9%	1,440,433	3.8%	225,019	3.2%	1,186,162	4.6%	527,334	5.0%
Nurse Practitioner	20,914,534	3.3%	5,748,315	3.6%	2,993,887	5.6%	1,875,406	5.0%	384,056	5.4%	1,736,995	6.7%	462,020	4.4%
Dentist	64,867,932	10.4%	8,568,981	5.3%	178,467	0.3%	50,349	0.1%	8,073	0.1%	23,529	0.1%	48,238	0.5%
Anesthesiologists	16,299,925	2.6%	6,863,668	4.3%	4,831,093	9.1%	3,888,158	10.3%	863,447	12.1%	3,944,589	15.3%	546,514	5.2%
All Others	164,297,047	26.4%	57,406,156	35.8%	15,647,914	29.3%	10,221,531	27.0%	2,019,129	28.3%	6,534,687	25.3%	4,360,474	41.2%

Source: MS, Vector One®: National (VONA) Extracted September 2012. Source File: VONA 2012-1613 Morphine IR and ER by Specialty 9-25-12.xls; VONA 2012-1613 Morphine IR and ER by Specialty 9-25-12.xls; VONA_2012-1613 hydromorphone specialties 09-25-12(1).xls; VONA 2012-1613 Oxycodone Combo Specialties 09-25-12(1).xls; VONA 2012-1613 Hydrocodone Specialties 09-25-12(1).xls

This analysis shows that prescribing patterns of opioid-containing analgesics vary by prescriber specialty. These patterns suggest that combination hydrocodone-containing analgesics may be used to treat more acute pain conditions (e.g. those treated in general practice, orthopedics and dentistry) than chronic pain conditions (those treated by anesthesiologists). DEPI/OSE examined this hypothesis by looking at duration of use.

1.2.4. Duration of therapy

The average days of therapy dispensed per prescription for combination hydrocodone-containing analgesics and combination oxycodone-containing analgesics in 2011 were very similar at about 14 days (**Figure 4**).

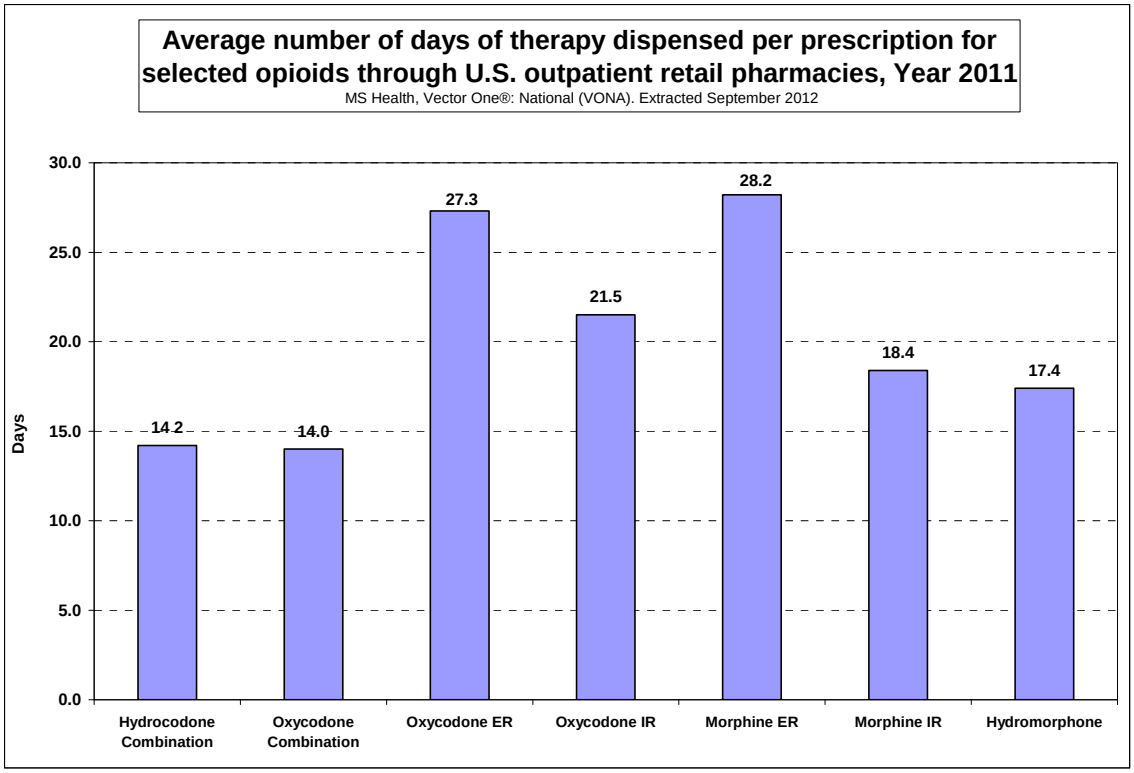

Figure 4 – Average Number of Days of Therapy Dispensed per Prescription for selected Opioids through U.S. Outpatient Retail Pharmacies, Year 2011. (Reproduced from the DEPI/OSE Drug Utilization Review)

For hydromorphone and IR morphine analgesics the duration of therapy was slightly higher at 17 and 18 days, respectively. For single-ingredient oxycodone products and ER morphine analgesics the duration of therapy were notably higher, ranging from 22-28 days. These findings also support the idea that combination hydrocodone-containing analgesics and combination oxycodone-containing analgesics are used to treat more acute pain conditions. However, the data are limited because they do not account for the fact that multiple prescriptions can be dispensed to the same patient over time and thus do not measure actual duration of use at the patient level. The data also rely on the average, or mean, which can be easily skewed by outliers.

To address some of these limitations, DEPI/OSE conducted a crude analysis of total days of therapy on a sample of patients, in which the duration of individual patients' prescriptions were added together over a two-year period (January 2010-December 2011), ignoring gaps in treatment. Then, DEPI/OSE examined the distributions of therapy days by deciles. The range of therapy for all selected opioid analgesics was similar, from 2 days up to the full two years. For combination hydrocodone-containing analgesics and combination oxycodone-containing analgesics, however, the median days of therapy was 8 days and 6 days, respectively – and the mean for each was skewed (as expected) to 45 days and 30 days, respectively (**Table 3**). The median values for immediate-release oxycodone products (19 days) and extended-release oxycodone products (31 days), provide additional support for OSE/DEPI's hypothesis that there

is more use of combination hydrocodone-containing analgesics and combination oxycodone-containing analgesics to treat acute pain conditions than to treat chronic pain conditions.

Table 3: Crude Days of Therapy for Selected Opioids in a Sample of Patients. Cumulative January 2010 through December 2011. (Reproduced from the DEPI/OSE Drug Utilization Review)

Crude days of therapy for selected opioids in a sample of patients
Cumulative January 2010 through December 2011

		Days of Therapy			
Regimen	Number of sample patients	Median	Average	Min	Max
HYDROCODONE COMBO	16,281,353	8	45.1	2	730
OXYCODONE COMBO	5,497,455	6	30.0	2	730
OXYCODONE IR	1,168,258	19	72.4	2	730
OXYCODONE ER	70,654	31	42.6	2	664

Source: Source Healthcare Analytics ProMetis Lx®, January 2010-December 2011, extracted January, 2011,
Source File: SHACPA 2009-2039 Hydrocodone Deciles 01-31-12 xls

Estimated Duration of Therapy by Deciles for a Sample of Patients on Hydrocodone Combination Products, Oxycodone Combination Products, Oxycodone ER, Oxycodone IR, January 01, 2010 through December 31, 2011 cumulative

		DECILES									
Regimen	Number of sample patients	1	2	3	4	5	6	7	8	9	10
HYDROCODONE COMBO	16,281,353	2 - 3	3 - 4	4 - 5	5 - 6	6 - 8	8 - 11	11 - 16	16 - 32	32 - 109	109 - 730
OXYCODONE COMBO	5,497,455	2 - 3	3 - 4	4 - 5	5 - 6	6 - 6	6 - 8	8 - 12	12 - 23	23 - 59	59 - 730
OXYCODONE IR	1,168,258	2 - 4	4 - 6	6 - 8	8 - 11	11 - 19	19 - 31	31 - 47	47 - 93	93 - 221	221 - 730
OXYCODONE ER	70,654	2 - 6	6 - 10	10 - 16	16 - 23	23 - 31	31 - 31	31 - 37	37 - 62	62 - 100	100 - 664

Source: Source Healthcare Analytics ProMetis Lx® , January 2010-December 2011, extracted January, 2011, Source File: SHACPA 2009-2039 Hydrocodone Deciles 01-31-12.xls

1.2.5. Indication for use

DEPI/OSE examined indications for use of combination hydrocodone-containing analgesics and compared it to other selected opioid analgesics (**Table 4**). DEPI/OSE used an office-based physician survey in which a sample of approximately 3200 physicians record all patient encounters during one typical workday per month, and then the data are weighted to make national projections. Diagnoses (coded to ICD-9) are linked to each drug product mentioned during a patient encounter, and then grouped into diagnostic categories (collapsed to 3-digit ICD-9 codes).

Table 4: Diagnosis Associated with Use (by grouped ICD-9 codes) for Selected Opioids as Reported by Office-Based Physicians in the U.S., Jan 2007-Nov 2011 cumulative. (Reproduced from the DEPI/OSE Drug Utilization Review)

Diagnoses Associated with Use (by grouped ICD-9 codes) for Selected Opioids as Reported by Office-Based Physicians in the U.S., Jan 2007-Nov 2011 cumulative										
	Hydrocodone Combo		Oxycodone Combo		Oxycodone IR		Morphine ER		Morphine IR	
	N(000)	%	N(000)	%	N(000)	%	N(000)	%	N(000)	%
Total Market	**2,850**	***100%***	**1,406**	***100%***	**566**	***100%***	**2,618**	***100%***	**407**	***100%***
Diseases of the Musculoskeletal System and Connective Tissue (710-739)	699	*25%*	287	*20%*	230	*41%*	1,781	*68%*	226	*56%*
Disease of Respiratory System (462-493)	594	*21%*	31	*2%*						
Fractures, Sprains, Contusions, Injuries (800-999)	547	*19%*	368	*26%*	43	*8%*	89	*3%*	15	*4%*
All others	360	*13%*	102	*7%*	13	*2%*	64	*2%*	27	*7%*
Follow up examinations	286	*10%*	198	*14%*	11	*2%*	113	*4%*	21	*5%*
Headaches and Nerve Pain (337-359)	98	*3%*	51	*4%*	213	*38%*	392	*15%*	81	*20%*
Fever and General Symptoms (780-789)	96	*3%*	53	*4%*	28	*5%*	64	*2%*	25	*6%*
Neoplasms (140-239)	70	*2%*	5	*0%*	31	*5%*	102	*4%*	2	*0%*
Disease of Genitourinary System (592-626)	62	*2%*	311	*22%*			11	*0%*	9	*2%*
Bacterial, Viral and Parasitic Infections (001-138)	39	*1%*	4	*0%*	1	*0%*	8	*0%*	2	*0%*

Encuity Research LLC. Physician Drug and Diagnosis Audit, Jan07-Nov11. Extracted January 2012, Source Files: PDDA 2009-2039 Hydrocodone, oxycodone, morphine, hydromorphone DX4 (new grouping) 01-20-12.xls; PDDA_2009-2039_Oxycodone_DX4_01-20-12(2).xls; PDDA_2009-2039_Morphine_DX4_01-20-12(1).xls

The most common diagnoses associated with the use of combination hydrocodone-containing analgesics included "Diseases of the Musculoskeletal System and Connective Tissue" (25% of total drug use mentions); "Diseases of the Respiratory System" (21% of total drug use mentions) and "Fractures/Sprains/Contusions/Injuries (19% of total drug use mentions). These diagnoses were similar to those associated with the use of combination oxycodone-containing analgesics, yet very different from those associated with the use of oxycodone IR and morphine products (IR or ER). The single-ingredient opioid analgesics were mentioned much more often in relation to "Diseases of the Musculoskeletal System and Connective Tissue (41-68% of total drug use mentions) and with "Headaches and Nerve Pain (15-38% of total drug use mentions). These data also appear to support the idea that combination hydrocodone-containing analgesics and combination oxycodone-containing analgesics are used to treat acute pain, whereas the single-ingredient opioid analgesics appear to be used more for treatment of chronic pain.

2. Abuse Liability Studies and Abuse Potential

In response to the most recent request of DEA for the re-analysis of the abuse related data on hydrocodone combination products, CSS conducted a review of the scientific literature, from 2003 to date, of the relative abuse potential in humans of hydrocodone (Schedule II) and hydrocodone combination products (Schedule III), (Zacny 2003, Zacny et al, 2005, Zacny and Gutierrez, 2008 and 2009, Walsh et al. 2008, Stoops et al. 2010).[5] This review showed that hydrocodone and hydrocodone in combination with other non-narcotic substances produced

[5] Walsh, S. L., Nuzzo, P. A., Lofwall, M. R., Holtman Jr, J. R., **2008**. The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abuses. Drug Alcohol Depend. 98, 191-202.
Zacny, J. P., **2003**. Characterizing the subjective, psychomotor, and physiological effects of hydrocodone combination product (Hycodan) in non-drug-abusing volunteers. Psychopharmacology 165, 146-156.
Zacny, J. P., Gutierrez, S., Bolbolan, S.A., **2005**. Profiling the subjective, psychomotor, and physiological effects of hydrocodone/acetaminophen product in recreational drug users. Drug Alcohol Depend. 78, 243-252.
Zacny, J. P., Gutierrez, S., **2008**. Subjective, psychomotor, and physiological effects profile of hydrocodone/acetaminophen and oxycodone/acetaminophen combination products. Pain Med. 9 (4), 433-443.
Zacny J. P., Gutierrez, S., **2009**. Within-subject comparison of the psychopharmacological profiles of oral hydrocodone and oxycodone combination products in non-drug-abusing volunteers. Drug Alcohol Depend. 101, 107-114.

similar effects to those of the typical mu-opioid agonists such as morphine, oxycodone or hydromorphone (Schedule II), in a dose-related manner. These effects include subjective opioid effects, such as "high" and "drug liking", as well as depending on the study population and product administered unpleasant effects, such as dizziness and increased rating of nausea. These studies showed that hydrocodone single entity and in combination produce subjective abuse-related effects at doses of hydrocodone bitartrate equal to or greater than 15 mg when taken orally.

These human abuse potential studies provided information on the relative abuse potential of hydrocodone to that of other opioids, such as morphine, oxycodone and hydromorphone.

All studies were crossover designs, placebo controlled, and enrolled non-opioid-dependent subjects. Some of the methodological variables differentiated these studies. These variables included the subject population studied, the various formulations of hydrocodone administered and routes of administration. The number of subjects included in these studies varied from nine to twenty, and some of the studies included subjects with prior history of recreational drug use, whereas others identified subjects with a prior history of opioid abuse or prescription opioid abuse. In all the studies, the reinforcing effects of several doses of either single entity hydrocodone compounded products, or combination with either acetaminophen or homatropine, were compared to the effects mediated by other opioids. The single entity products, as well as the high strength hydrocodone combination products studied are not currently marketed products in the United States.

It is relevant to mention that human abuse potential studies measure the relative abuse potential of a drug when compared to another drug of abuse. However, there are several factors that may impact the abuse of a product that are not measured under the conditions of these studies. Among these factors are those intrinsic to the formulation, such as a new formulation with a faster or delayed onset of action; and those that go beyond the properties of the formulation and that include, among others, individual subject differences, prescribing patterns, the availability of other opioid formulations, and fads.

Though I recognize that there are several methodological variables that may have impacted the outcomes and the interpretation of the data, I note that the subjective opioid effects associated with a drug's potential for abuse, such as euphoria and liking, as well as the adverse effects produced by hydrocodone are dose-related. These effects are observed at doses of hydrocodone bitartrate equal to or greater than 15 mg. I should also point out that although combination products containing up to 25 mg of hydrocodone bitartrate (equivalent to 15 mg hydrocodone base) would fall under Schedule III of the CSA, currently the highest strength of hydrocodone combination products is of 10 mg (equivalent to 6 mg hydrocodone base) of hydrocodone bitartrate. Thus far, manufacturers have limited themselves to the development of formulations within that range, which is less than the amount allowed by the CSA for a Schedule III product. Based on the available data showing that reinforcing effects associated with hydrocodone manifest at doses greater than 15 mg hydrocodone bitartrate, if a combination product containing doses of hydrocodone bitartrate greater than 15 mg of bitartrate salt per dosage unit were to be developed, I would recommend requiring clinical studies to fully evaluate the abuse potential of such a product.

3. Actual Indicators of Abuse (Epidemiological Data)

Measuring drug abuse-related health outcomes, including overdose and death, for specific prescription drug products is quite challenging given the absence of comprehensive national data sources designed specifically to collect this information. Currently, there is no single national data system from which both *numerators* (events representing outcomes related to the abuse of a specific prescription drug) and *denominators* (a measure of the population exposed or at risk for abuse from a specific prescription drug) are ascertainable. Therefore, current surveillance efforts rely on capturing numerators and denominators from separate sources, each of which has its own limitations. These numerators and denominators are used to calculate risk estimates ("abuse ratios" or "abuse rates" which are not actually rates), which lack precision inherent to putting together numbers from variable sources. Both DEA and FDA have been challenged in their respective risk assessments by the paucity of data which allow for accurate attribution of risk of abuse to *specific* prescription drug products, which is necessary for comparative risk assessment.

As stated by DEPI/OSE in their review, the epidemiological assessment of abuse associated with the use of combination hydrocodone-containing analgesics (Schedule III) relative to other products in Schedule II relies on:

- the selection of appropriate *comparator products*,
- the selection of the most informative and granular drug abuse-related health outcomes (*numerators*),
- the selection of optimal *denominators* used for putting numerators into the appropriate context.

In their review DEPI/OSE discussed each of these issues separately, and then described the findings of their analyses, and how they differed from DEA's analyses.

3.1. Comparators

In DEA's analysis, oxycodone products were selected as the comparator products in the epidemiological assessment; DEPI/OSE agreed that oxycodone is an appropriate comparator to hydrocodone. In an earlier assessment, FDA had also used propoxyphene[6] (Schedule IV) and codeine (Schedule III-V) as additional comparator drugs, but DEPI/OSE agreed that the utility of using these additional comparators was limited by the data available on these drug products. As single ingredients, hydrocodone and oxycodone are both Schedule II, though there are currently no approved single-ingredient hydrocodone products. (Currently, marketed hydrocodone-containing combination products are in Schedule III, while combination oxycodone-containing products are in Schedule II.) They are both mu-opioid agonists, they are equipotent on a milligram basis as oral analgesics and approximately equipotent on milligram basis in abuse liability. In terms of availability, 90% of both combination hydrocodone-containing analgesics and combination oxycodone-containing analgesics on the market contain acetaminophen. Additionally, both hydrocodone and oxycodone are drugs that have been on the market for many years and have similar approval dates and more likely to have similar abuse histories. Lastly, oxycodone is an opioid product that also has high sales volume; it is expected that larger projected estimates could result in more precise measures, although it is not possible to construct confidence intervals around abuse rates with numerators and denominators derived from different sources.

There are differences between hydrocodone and oxycodone, however, which still make comparisons between these two drugs challenging. From the drug utilization analysis presented earlier, it can be seen that oxycodone is available not just as a combination product but also as single-ingredient products – both immediate and extended release – and these single-ingredient products contain more opioid per dosage unit than the combination products. Although the majority of dispensed prescriptions for oxycodone are for combination products (69%), those prescriptions represent only 27% of the amount of total oxycodone dispensed in kilograms of opioid salt. This is due to the fact that the single-ingredient oxycodone products, representing only 31% of all oxycodone prescriptions, contain more opioid and actually represent 73% of all oxycodone dispensed as measured in kilograms of opioid salt.[7] Hydrocodone is currently marketed only as a combination product. Not surprisingly, there are differences in how the single-ingredient oxycodone products and the combination oxycodone-containing products are used clinically, with the single-ingredient products appearing to be used for longer duration in relation to diagnoses suggesting treatment of chronic, rather than acute, pain.

Although DEPI/OSE agrees with DEA that oxycodone is an appropriate comparator for hydrocodone, there remain differences that need to be accounted for in any analysis that compares these two currently available products. DEPI/OSE found that by carefully selecting the appropriate numerator and denominator for estimating risk, we could improve our ability to take these differences into account.

3.2. - Numerators

[6] Propoxyphene was an approved product at the time of the analysis. It has since been withdrawn from the market for safety reasons.

[7] Cited from DEA's analysis- based on data from IMS Health, IMS National Sales Perspectives (January 2002-December 2007), Retail Channels, Data Extracted September 2008.

In their review DEPI/OSE lists the following data sources, as those available to assess morbidity and mortality associated with abuse of prescription drugs (*numerators*) and used in estimating risk:

- ***The National Poison Data System (NPDS)*** – formerly known as the Toxic Exposure Surveillance System (TESS), NPDS data are compiled by the American Association of Poison Control Centers in cooperation with the majority of poison control centers across the U.S. NPDS data are based on the capture of calls to poison control centers from consumers and health care professionals. NPDS is the only near real-time comprehensive poisoning surveillance database in the U.S. and holds more than 50 million poison exposure case records (e.g., calls) with more than 2 million new records added each year.

- ***The Drug Abuse Warning Network (DAWN)*** – DAWN was a public health surveillance system that monitored a selected, nationally representative sample of emergency departments (ED) across the U.S. to collect data on drug abuse related visits. At one time, DAWN also collected non-nationally representative data on deaths investigated by a select group of state medical examiners and coroners to assist in tracking the impact of drug abuse. DAWN ceased data collection at the end of 2011, but efforts are underway to continue collecting similar data through other national hospital surveys, with minimal interruption.

- ***The Florida Department of Law Enforcement (FDLE)*** – FDLE is a source of medical examiner data from the state of Florida that includes deaths in which a drug is either listed specifically as the cause of death, or was demonstrated to be present in the body at the time of death. This data source includes only deaths occurring in Florida.

Other numerator data were also used by DEA and by FDA to estimate the risk of abuse associated with combination hydrocodone-containing products and comparators. These include survey data from the ***National Survey on Drug Use and Health (NSDUH),*** and ***Monitoring the Future (MTF).*** NSDUH provides information on the prevalence, patterns and consequences of the use and abuse of a number of illicit and prescription drugs in the general U.S. civilian non-institutionalized population, aged 12 years and older. This annual face-to-face survey provides national estimates of rates of use, numbers of users and other measures related to drugs, alcohol and tobacco products. MTF is an ongoing effort of the National Institute on Drug Abuse which consists of a questionnaire-based survey of drug use, specifically among a representative sample of high school students in the U.S.

The use of these numerators is limited by the fact that the majority of the existing drug abuse and diversion data sources do not provide information on specific products, formulations (immediate vs. extended release), and composition (single ingredient vs. combination products), which are key factors for oxycodone products. The only data source that can provide details on specific composition of products (single ingredient vs. combination) and formulations (data on immediate vs. extended release is provided to FDA directly) is the DAWN data; it also provides information on whether the ED visit was related to abuse or to an adverse event related to therapeutic use.

By focusing on national estimates of ED visits, DAWN provides data reflecting serious events that result in morbidity and possibly mortality in relation to drug abuse, which reflects true public health impact. In contrast, NPDS data provide detail on drug substances but not on specific formulations (e.g. may report oxycodone use, but not whether single-ingredient or combination, and not whether immediate or extended release). Calls to NPDS may or may not result in actual medical events requiring treatment, and may be the result of accidental ingestion rather than abuse. And although FDLE focuses on deaths related to drug abuse, which is an important public health outcome, the drug data are limited to substance and not specific composition or formulation, as it is based on toxicology screens. NSDUH and MTF reflect data on abuse in general, and cannot address questions about specific product composition and formulations (although NSDUH can differentiate OxyContin use from other oxycodone-containing products); these surveys also do not focus on the public health impact of abuse – which is largely related to morbidity and mortality.

Therefore, I agree with DEPI/OSE's view that DAWN data provide the most robust and useful numerator data for assessing the abuse of combination hydrocodone-containing products, as well as the multiple formulations of oxycodone, and therefore FDA focuses its primary analysis on that data source.

3.3. - Denominators

The use of a different set of *denominators* to estimate the rates of drug-related health outcomes was one of the most important points in the reanalysis submitted by DEA to FDA**.** The denominators used in the DEA's reanalysis were ***Total Patient-Days of Therapy*** and ***Total Amount of Substance Distributed (sales in kg).***

There are multiple denominators that have been used for providing a context for abuse risk estimation. Those considered by DEA and by FDA in their analyses of abuse of combination hydrocodone-containing products include:

(1) Total U.S. population
(2) Total Number of Prescriptions
(3) Total Patient-days of Therapy
(4) Total Amount of Substance Distributed (in kilograms of the salt)
(5) Total Number of Extended Units (i.e. pills or tablets) dispensed
(6) Total Number of Patients receiving a dispensed prescription

There is no one denominator that adequately reflects the amount of hydrocodone and oxycodone circulating in the marketplace, while also allowing for inter-drug comparisons that take into account the differences in composition, formulation, quantity dispensed and the amount of active drug in each dosage unit dispensed, that were pointed out earlier. Each of the denominators examined offers a unique advantage over the others, yet the use of each different denominator generates different results when comparing hydrocodone to oxycodone (See Attachment for Review).

DEPI/OSE considered the various denominators, along with their strengths and limitations. In its 2008 analysis, ***Total Number of Prescriptions*** was used as the denominator. This measure, however, did not account for substantial differences in the dosage units dispensed per prescription of various opioids, so DEPI/OSE explored the use of other denominators for its 2011 analysis. DEPI/OSE found that ***Total Number of Extended Units Dispensed*** as a denominator likely provided the best metric of patient exposure-based risk, because each tablet can be considered an "exposure opportunity" representing the total opioid available for abuse. This measure also adequately accounts for the variability between hydrocodone and oxycodone with regard to dosage units dispensed per prescription and also differences related to product formulation and composition.

The use of ***Total Amount of Substance Distributed (in kilograms)***, which was favored by DEA as a denominator, has the advantage of accounting for drug diverted from the supply chain prior to dispensing and therefore seems very desirable. Upon further examination, however, DEPI found that this denominator did not adequately account for differences between opioids, particularly between hydrocodone and oxycodone, with regard to the amount of opioid per dosage unit on a milligram basis. For example, hydrocodone is only available as an analgesic commercially as a combination product with acetaminophen containing between 2.5 mg to 10mg of hydrocodone per dosage unit. Based on the most frequently prescribed strengths, we estimate that each gram of hydrocodone sold represents about 440 dosage units or tablets. In contrast, oxycodone is available both as a combination product and as single-ingredient products, of both immediate and extended release, ranging from 2.5mg to 80mg of oxycodone per dosage unit. Again, based on the most frequently prescribed strengths, we estimate that each gram of oxycodone sold represents about 73 dosage units or tablets. Thus, a kilogram of one opioid is not equal to a kilogram of another, with regard to the amount of potentially abuseable product that is introduced into the marketplace.

3.4. Summary and key findings of the DEPI/OSE review

DEPI/OSE's analysis (described in detail in the review dated Feb 9, 2011) focused primarily on DAWN data as the numerator and Total Number of Extended Units Dispensed as the denominator, using combination oxycodone-containing analgesics as the comparator for combination hydrocodone-containing analgesics. The key results are:

- DEPI's analysis of DAWN ED Visits demonstrated that when using Total Number of Extended Units Dispensed as the denominator, in 2009 the rate of ED visits mentioning combination oxycodone-containing analgesics (24 per million extended units dispensed) was higher than that corresponding for combination hydrocodone-containing analgesics (11 per million extended units dispensed), demonstrating a risk profile that is less favorable for combination oxycodone-containing analgesics. The rate for oxycodone single-ingredient products (IR or ER) were much higher at 59 per million extended units dispensed).

- DEPI/OSE's analysis of NPDS calls for toxic exposure to combination hydrocodone-containing products compared to any oxycodone-containing products (NPDS cannot reliably distinguish between product formulation and composition) demonstrated that in

2006, there were 3.58 toxic exposures/million extended units dispensed for combination hydrocodone-containing analgesics compared to 4.96 toxic exposures/million extended units dispensed for oxycodone products. This pattern of combination hydrocodone-containing analgesics having lower rates than oxycodone products was consistent no matter what denominator was used.

- NSDUH- The rates of past-year hydrocodone initiators[8] in comparison to oxycodone initiators were found to be slightly higher when using Total Number of Extended Units as the denominator (0.24 per million extended units dispensed vs. 0.20 per million extended units dispensed respectively), and slightly lower when using Total Number of Patients as the denominator (32.3 per million patients receiving prescriptions vs. 34.3 per million patients receiving prescriptions). These findings suggest that initiation of non-medical use of combination hydrocodone-containing products and combination oxycodone-containing products[9] is similar.

- DEPI/OSE did not conduct its own analysis of MTF data, but cautions that MTF data must be interpreted in light of the large number of prescriptions dispensed for combination hydrocodone-containing products, which were not accounted for in DEA's analysis. The higher prevalence of use of combination hydrocodone-containing products (Vicodin) reported by high school students (ranging from 2.5-10.5% by grade level) is likely to be a function of the larger number of prescriptions for combination hydrocodone-containing products than for oxycodone products (prevalence of use ranging from 1.3-5.5% by grade level). DEPI/OSE's view is that the increased availability of combination hydrocodone-containing products results in increased opportunities for experimentation by adolescents, making MTF data difficult to use to make inferences about the risk profile of combination hydrocodone-containing products and oxycodone products. Interestingly, more recent MTF data shows for the first time a decrease in the annual prevalence of non-medical use of Vicodin (8%) reported by 12th graders in year 2010; similar rates were found for 2011.

In summary, the use of a different set of *denominators* to estimate the rates of drug-related health outcomes constitutes the most important point in the reanalysis performed by DEA**.** DEPI/OSE analyses showed abuse rates for combination hydrocodone-containing analgesics using *measures of mortality and morbidity* in the *numerator* and *Total Number of Extended Units Dispensed* in the *denominator* are lower than those for combination oxycodone-containing analgesics. When using *survey data* as the *numerator*, the abuse rates between combination hydrocodone-containing products and oxycodone-containing products are similar. In addition, DEPI/OSE did not find data to support DEA's assertion that the addition of acetaminophen to hydrocodone tablets does not deter abuse. Since hydrocodone is not available as a single-ingredient product, direct evidence could not be obtained. However, other analgesics are used both in combination and as single-ingredient products (oxycodone and tramadol). Available evidence suggests that abuse rates are lower for the combination products when using *DAWN data* (*numerator*) and *Total Number of Extended Units Dispensed* (*denominator*). For combination oxycodone-

[8] An initiator is a respondent reporting the non-medical use of the drug in question for the first time within the past year.
[9] NSDUH allows for differentiation between OxyContin specifically and other oxycodone-containing products.

containing products vs. single-ingredient oxycodone products, there were 24 ED visits per million extended units dispensed vs. 59 ED visits per million extended units dispensed in 2009, respectively. For combination tramadol-containing products vs. single-ingredient tramadol products, there were 2.8 ED visits per million extended units dispensed vs. 4.5 ED visits per million extended units dispensed in 2004, respectively. DEPI/OSE's view is that the situation would likely be similar for hydrocodone products, if a single-ingredient product were commercially available.

I should point out that there are limitations inherent to DEPI/OSE's analyses that should be considered when interpreting the results. Given that the numerators and denominators are derived from different sources, and are put together to calculate "ratios", it is not possible to calculate confidence intervals nor to conduct statistical testing to determine significant differences. As mentioned previously, none of the denominators available is ideal; DEPI/OSE chose *Total Extended Units Dispensed*, which did not account for drug diverted from the supply chain prior to dispensing, which is a limitation. The analyses completed in DEPI/OSE's review exclusively focused on combination hydrocodone-containing *analgesic* products and *excluded* combination hydrocodone-containing *antitussive* products. However, DEPI/OSE conducted a separate review on combination hydrocodone-containing antitussive products and found little evidence of abuse in 2009 (based on data through 2007); an update to include data from 2008 and 2009 found too few abuse cases in DAWN to report (See Attachments). Therefore, the exclusion of antitussive products does not appear to impact the estimates of abuse relating to combination hydrocodone-containing products, as the majority of abuse appears to relate to analgesics.

Therefore, I concur with DEPI/OSE's conclusion that there is insufficient evidence to support DEA's finding that combination hydrocodone-containing products have a similar potential for abuse to oxycodone products. It is clear, however, from DEPI/OSE analyses that combination hydrocodone-containing analgesics are widely abused, but no objective threshold exists to correlate levels of abuse with the level of scheduling. From a public health viewpoint, abuse of combination hydrocodone-containing analgesics poses a significant risk to the community; however this risk might be commensurable with the Schedule III status of these products.

4. Potential Impact of Re-scheduling Hydrocodone Containing Products to Schedule II of the CSA.

The rescheduling of hydrocodone combination products (both analgesic and antitussives or cough suppressant products) would lead to additional regulatory requirements at the level of manufacturers, distributors, dispensers such as pharmacies and physicians, and importers and exporters, which may also impact patient access to these products.

The purpose of scheduling substances under the CSA is to minimize abuse and diversion while affording appropriate therapeutic access. Each schedule under the CSA includes a set of regulations that are most restrictive for the Schedule I and II substances and are relatively less restrictive for the Schedule III to V drugs, respectively. Drugs in Schedule I have no accepted medical use in treatment in the United States. Depending on the Schedule (II-V), controls may include manufacturing quotas, varying degrees of manufacturing and distribution site security

requirements, dispensing and prescribing limitations, a range of record-keeping and reporting requirements, and import/export regulations. Prescribers, dispensers, drug manufacturers, and distributors are required to register with the DEA.

Since hydrocodone substance is already in Schedule II, manufacturing quotas for this substance are established annually by the DEA. As expanded in the following subsections, the rescheduling of hydrocodone combination products would impose additional regulatory requirements on manufacturers, distributors, dispensers such as pharmacies and physicians, importers and exporters.

4.1. Manufacturers

Schedule II controls require that substances be transferred between registrants via a triplicate, sequentially-numbered DEA form (DEA Form 222 Official Order Form) or its electronic equivalent, while invoices, packing slips or other records are sufficient to transfer Schedule III-V drugs among registrants.

Manufacturers and distributors must secure Schedule II substances in a safe, steel cabinet or vault while Schedule III-V substances may be stored in a less secure controlled substance cage or other enclosure.

4.2. Prescribers and Dispensers

Depending on the State, mid-level practitioners such as physician assistants, nurse practitioners and optometrists are not authorized to prescribe Schedule II substances. Therefore, these practitioners may no longer be able to treat pain with hydrocodone combination products if these products were re-scheduled to Schedule II.

With limited exceptions for emergency oral prescriptions, prescriptions for schedule II substances must be handwritten, and pharmacies must have the original prescriptions in-hand before dispensing. Prescriptions for Schedule III-V may be in a written, electronic, oral (so long as it is promptly reduced to writing), or faxed format. Schedule II prescriptions cannot be refilled; however, a practitioner may issue multiple prescriptions authorizing the patient to receive up to a 90 day supply of a schedule II controlled substance provided that certain requirements are met. Schedule III-V prescriptions can be refilled up to five times within a six month period.

4.3. Patients

The largest concern with up-scheduling of the hydrocodone combination products is the potential impact on patient access to adequate pain management. Schedule II products require twice as many visits to the healthcare provider as Schedule III products. Schedule II products may only be prescribed for one month at a time, although prescribers may give patients three months worth of prescriptions, and cannot be phoned into the pharmacy (except for emergency situations), while prescriptions for Schedule III products can be written with up to five refills for a total of six months and can be phoned into the pharmacy if promptly reduced to writing. For patients in

pain, particularly those at a distance from their healthcare provider, this represents a physical and financial burden.

Physicians may opt for other analgesic options over hydrocodone combination products if these products were up-scheduled. Schedule III options include codeine in combination with acetaminophen or aspirin, however, it is not as frequently prescribed as hydrocodone combinations likely due to less efficacy and more adverse events such as nausea and constipation. Congress placed drugs containing not more than 50 mg of morphine per 100 milliliters or per 100 grams with one or more active non-narcotic ingredients in Schedule III of the CSA, but there are no such products currently approved in the U.S. Analgesics under Schedule IV such as butorphanol and pentazocine, and currently unscheduled products are generally recognized to be less effective for moderate to severe pain than hydrocodone combination products and the Schedule II opioids. Dextropropoxyphene products were removed from the market in 2010 and are no longer approved for marketing in the U.S.

There may also be an increase in use of the NSAIDs, although they are generally not adequate for treatment of severe acute postoperative pain and patients with chronic pain are usually treated with opioid analgesics only after non-opioid options are exhausted. While NSAIDs lack the unwanted central nervous system adverse effects of opiates such as respiratory depression, euphoria and physical dependence, they are associated with many potentially serious adverse events involving the gastrointestinal, cardiovascular, renal and hepatic systems. Other adverse effects of NSAIDS include anemia, serious skin rashes, fluid retention, congestive heart failure, and edema. NSAIDs are also inappropriate for use during the third-trimester of pregnancy due to the risk for premature closure of the ductus arteriosis.

Alternatively, prescribers may prescribe single-entity Schedule II opioids more frequently once hydrocodone/acetaminophen combination analgesics no longer represent a lower burden. As described above, the single-entity Schedule II opioid analgesics such as oxycodone, tend to have a higher frequency of emergency department mentions through DAWN.

Hydrocodone combination products approved for cough suppression such as Hycodan, a tablet formulation of hydrocodone 5 mg with a low dose of homatropine (1.5 mg), would also be re-scheduled to Schedule II, leaving codeine containing products as the sole option of Schedule III cough suppressants.

The unintended consequences of changes affecting prescribing requirements were observed at the State level, when in 1989, the State of New York imposed a triplicate program for the widely used benzodiazepine agents. Ross-Degnan *et al*. (2004)[10] and Simoni-Wastila *et al*. (2004)[11]

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[10] Ross-Degnan, D., Simoni-Wastilla, L, Brown, J. S., Gao, X., Mah, C., Cosler, L. E., Fanning, T., Gallagher, P., Saltzman, C., Shader, R. I., Inui, T. S., Soumerai, S. B., **2004**. A controlled study of the effects of state surveillance on indocators of problematic and non-problematic benzodiazepine in a Medicaid population. Int. J. Psychiatry Med. 34, 103-123.

[11] Simoni-Wastila, S., Ross-Degnan, Mah, C., Gao, X., Brown, J., Cosler, L.E., Fanning, T., Gallagher, P., Salzman, C., Soumerai, S.B., **2004**. A retrospective data analysis of the impact of the New York triplicate prescription program on benzodiazepine use in Medicaid patients with chronic psychiatric and neurologic disorders. Clin. Ther. 26, 322-336.

showed that the New York program reduced use of benzodiazepines among chronically ill patients for whom these agents represented effective treatments. These investigators also concluded that the largest reduction in benzodiazepine use was seen among patients with seizure disorders. Furthermore, the authors concluded that this program did not reduce the problematic use of these drugs.

III. Conclusions

Taking under consideration all data provided by CSS, DAAAP, DEPI/OSE, I conclude that abuse potential is a complex determination with many dimensions and no single measure of abuse potential is ideal. Substances are scheduled under the CSA based on their abuse potential, and as such Congress placed hydrocodone combination products in Schedule III of the CSA. However, there is no single test or assessment procedure that, by itself, provides a full and complete characterization or allows for quantification of the abuse potential of a substance, or like in this case, of combination products. Overall a scientific and comprehensive evaluation of the relative abuse potential of hydrocodone combination product needs to be weighed in the final recommendation of whether to up-schedule or not these products. This evaluation has to take under consideration the pharmacology and reinforcing effects of hydrocodone, the medical use and availability, epidemiological findings used as surrogates of the levels and scope of abuse, as well as measures of the consequences of abuse of the hydrocodone combination products.

The question that still remains is how to reduce the levels of abuse of hydrocodone combination products. Alternatives to up-scheduling may also decrease the levels of abuse and misuse of these products and may prove beneficial and effective in addressing abuse and misuse of hydrocodone combination products. Educational efforts as well as the use of Prescription Drug Monitoring Programs (PDMPs) may have an effect in curtailing the abuse of hydrocodone combination products in the context of prescription drug abuse in general.

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

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Drug Name(s):	hydrocodone containing products
Submission Number:	various
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EXECUTIVE SUMMARY

The Controlled Substances Staff (CSS) is evaluating the abuse of respiratory (cough and cold) hydrocodone products that, to date, have been marketed without approval. In support of that evaluation, the Office of Surveillance and Epidemiology (OSE), Division of Epidemiology (DEPI) has been requested to evaluate data from the Drug Abuse Warning Network (DAWN) as well as prescription utilization data for all hydrocodone containing products.

This analysis uses dispensed prescriptions for hydrocodone containing products using IMS Health, Vector One®: National (VONA) and DAWN, a public health surveillance system that examines drug related emergency room visits to conduct its analysis.

National estimates were provided for emergency department (ED) visits associated with hydrocodone containing products stratified into: analgesic products, and respiratory products. Two types of ED visits associated with hydrocodone containing products were provided: adverse reaction, and all misuse/abuse (AllMA) were examined. An adverse reaction ratio and an "abuse ratio" were calculated by dividing the number of ED visits for each event by 10,000 prescriptions. Lastly, the number of non-medical use ED visits per adverse reaction ED visits (i.e. therapeutic use) was calculated to examine reasons why patients arrive in the ED, i.e. is it for non-medical or for therapeutic reasons.

The number of AllMA ED visits (n=245,297) as well adverse reaction ED visits (n=182,182) associated with analgesic hydrocodone products is large when compared to the total number of ED visits associated with respiratory hydrocodone products, (n=10,374). After adjusting for drug utilization however, these differences attenuate somewhat for adverse reaction ED visits (4.1/10,000 prescriptions for analgesic products vs. (1.9/10,000 prescriptions for respiratory products) and remain large for AllMA visits (5.5/10,000 prescriptions for analgesic products vs. 0.5/10,000 prescriptions for respiratory products.)

Using the limited evidence found in DAWN, the abuse of respiratory hydrocodone products appears to be lower than for analgesic hydrocodone products. Given significantly lower rates of drug utilization and evidence that some albeit much lower, abuse ratios were found with these products, OSE/DEPI makes the following recommendations for additional studies:

1) Abuse liability studies should be required of the sponsors submitting NDA's
2) Conducting these studies post-approval is appropriate
3) Without more information on the different molecular entities, the studies should be conducted on all respiratory hydrocodone containing products

1 BACKGROUND

1.1 INTRODUCTION

The Controlled Substances Staff (CSS) is evaluating the abuse of respiratory hydrocodone products that, to date, have been marketed without approval. In support of that evaluation, the Office of Surveillance and Epidemiology (OSE), Division of

Epidemiology (DEPI) has been requested to provide data from the Drug Abuse Warning Network (DAWN) as well as prescription utilization data for all hydrocodone containing products grouped as respiratory (cough/cold) and analgesic products for years 2004 through 2007.

The rationale for this request was in response to the Regulatory Briefing: Abuse Liability Testing for Hydrocodone Combination Products held on June 12, 2009. CSS was consulted on NDAs for hydrocodone cough cold combination products currently under review in the Division of Pulmonary and Allergy Products (DPAP). CSS believes that abuse potential studies should be performed on the hydrocodone products to support labeling and appropriate scheduling.

This recommendation, however, raised questions regarding whether to require abuse potential studies on hydrocodone combination products, and the regulatory briefing was conducted to answer the following questions:

1) Should abuse potential assessment be required for hydrocodone containing combination products for cough/cold/allergy indications?

2) If so, should the abuse potential assessment be required for approval or performed post-approval?

3) Should abuse potential assessment be required for all hydrocodone containing combination products for cough/cold/allergy indication or on a case by case basis?

At the regulatory briefing, it was determined that the sponsors of these products should be required to conduct abuse liability studies. These studies could be conducted post-approval and that the requirement for abuse potential assessment would be required on a case by case basis.

This analysis focuses on current epidemiological data of non-medical use of hydrocodone containing products using data obtained from the Drug Abuse Warning Network (DAWN) and drug utilization data obtained from IMS, Vector One®.

2 METHODS AND MATERIALS

2.1 DATA AND INFORMATION SOURCES

2.1.1 IMS Health, Vector One®: National (VONA)

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

We examined total dispensed prescriptions for hydrocodone containing products using IMS Health, Vector One®: National (VONA) (see Appendix 1 for full description) for calendar years 2004 through 2007.

2.2 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 (ED) 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.

2.3 CRITERIA USED

2.3.1 Outpatient Dispensed Prescriptions -- VONA

Table A.1 in the Appendix shows the total number of prescriptions dispensed in the outpatient retail setting (mail order excluded) for hydrocodone containing products. During year 2007, approximately 133 million prescriptions were dispensed for products containing hydrocodone of which approximately 123 million (92%) were dispensed for hydrocodone analgesic combinations and 10 million (7.7%) for hydrocodone cough and cold products. For both hydrocodone analgesic and hydrocodone cough and cold products, the number of prescriptions dispensed has increased by 23% and 9%, respectively, from year 2004 to 2007.

2.3.2 Drug Abuse Warning Network (DAWN)

CSS requested and obtained national estimates of drug related ED visits for hydrocodone containing for the years 2004 – 2007. Estimates were provided for ED visits associated with hydrocodone containing products broken out into three different categories: analgesic, respiratory products as well as estimates for both analgesic and respiratory (cough and cold) products combined. The drug combinations that were included in each of these categories can be found in Table A.3 of the Appendix.

One of the data elements recorded in DAWN includes “type of case”. Specific types for DAWN ED visits include suicide attempts, overmedication, adverse reactions, accidental ingestions, malicious poisoning, and patients seeking detoxification or drug abuse treatment and drug abuse and misuse, entered as “other”.

Three types of ED visits associated with hydrocodone containing products were provided: adverse reaction, all misuse/abuse (AllMA) and nonmedical use of pharmaceuticals (NMUP). AllMA and NMUP are constructs that combine various types of cases recorded in DAWN. NMUP: includes: ED visits where the patient exceeded prescribed or recommended dose i.e. overmedication, used drugs prescribed for another person, malicious poisoning (always very low numbers) or substance abuse which is categorized by “other”. AllMA is a more comprehensive category than NMUP; it includes all NMUP visits plus any visits where hydrocodone was present with an illicit drug or with alcohol.

Adverse reaction visits are drug-related ED visits that are the consequences of using a prescription or over-the-counter drug for therapeutic purposes. It includes ED visits related to adverse drug reactions, side effects, drug-drug interactions, and drug-alcohol interactions. Adverse reactions that involve a pharmaceutical with an illicit drug are exceptions and are excluded from this category.

It is important to note that, in DAWN, national estimates are not provided for all the data requested. If the relative standard error (RSE)[1] is greater than 50, national estimates cannot be provided because the confidence intervals are too large and there is too much imprecision in the estimate. Estimates were requested by ten-year age bands and for case disposition, in many cases, these data were suppressed due to RSE's greater than 50. As a result, ages of patients as well as case disposition were not analyzed because there were too many suppressed estimates. Likewise, there were numerous missing values for visits considered to be NMUP visits so AllMA visits (as well as adverse reaction) were used for this analysis.

2.4 ANALYSIS TECHNIQUES/STEPS

This analysis utilizes data obtained from the DAWN as well as data on drug utilization obtained from IMS Health, Vector One® National.

Two types of ED visits were examined in this analysis to determine reasons why patients who use hydrocodone-containing products go to the ED: therapeutic- (adverse reaction) or non-medical- (misuse/abuse) related visits or both. Since the number of emergency room visits may be the result of greater drug utilization, i.e. greater drug exposure, drug utilization data were incorporated into this analysis. An "abuse ratio" was calculated by dividing the number of ED visits by 10,000 prescriptions. A similar ratio was computed for adverse reactions by dividing the number adverse reaction ED visits by 10,000 prescriptions.

Lastly, the number of non-medical use ED visits per adverse reaction ED visits (i.e. therapeutic use) was calculated to examine the reason why patients arrive in the ED primarily i.e. is it non-medical use or is for therapeutic reasons. There were large differences in the number of adverse reactions reported in 2004 compared to other years; these differences are likely the result of more training for the medical extractors collecting these data after the first year (2004) on the major changes implemented to the DAWN database.

3 RESULTS

Table 3.1 shows the national estimates of "AllMA" (i.e. all misuse/abuse) ED visits associated with analgesic and respiratory hydrocodone containing products as well as "abuse ratios' for each category. There were 46,924 ED visits in 2004. The number increased (65%) to 77,560 visits in 2007 for analgesic hydrocodone products. The number of AllMA ED visits associated with respiratory hydrocodone products ranged from 389 ED visits in 2004 to 616 ED visits in 2007. It is important to note, that the RSE for the estimates for respiratory combination products in 2004 – 2006 were too large to produce confidence intervals and the estimates themselves cannot be regarded as precise ones.

[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.

The numbers of prescriptions dispensed for analgesic hydrocodone products increased from over 100 million prescriptions in 2004 to more than 133 million prescriptions in 2007 (21%). The number of prescriptions for respiratory hydrocodone products were considerably lower, approximately nine million prescriptions in 2004 to over 10 million in 2007.

The "abuse" ratios, for analgesic hydrocodone products increased from 4.3 ED visits per 10,000 prescriptions in 2004 to 5.8 ED visits per 10,000 prescriptions in 2007 (35%). For respiratory hydrocodone products, the ratios were somewhat variable and considerably lower, it ranged from a low of 0.3 ED visits per 10,000 prescriptions in 2005 to the highest ratio being 0.9 ED visits per 10,000 prescriptions in 2006. The results show an increasing trend for AllMA ED visits over time despite adjusting for use with respiratory products containing hydrocodone,

Table 3.1: National Estimates of all abuse/misuse (AllMA) ED Visits Reported in DAWN and Number of ED Visits per 10,000 Prescriptions for Analgesic and Respiratory Hydrocodone Containing Products -- 2004 -2007

AllMA ED Visits	***2004***	***2005***	***2006***	***2007***
Analgesic and Respiratory Products	**46,924**	**56,037**	**67,043**	**77,560**
95% CI	(35,536, 58,312)	(40,319, 71,756)	(52,019, 82067)	(59,306, 95,814)
Analgesic combinations	46,535	55,704	66,114	76,945
95% CI	(35,191, 57,878)	(39,939, 71,467)	(51,212, 81,015)	(58,712, 95,178)
Respiratory combinations	*389*	*333*	*929*	616
95% CI	...	...	...	(116, 1,115)
Hydrocodone Prescriptions				
Analgesic and Respiratory Products t	**109,738,552**	**120,091,780**	**126,492,450**	**133,228,908**
Analgesic Products	100,322,326	108,207,757	115,680,718	122,929,534
Respiratory Products	9,416,226	11,884,023	10,811,732	10,299,374
Abuse Ratios*				
Analgesic and Respiratory Products	**4.3**	**4.7**	**5.3**	**5.8**
Analgesic Products	4.6	5.1	5.7	6.3
Respiratory Products	0.4	0.3	0.9	0.6

*abuse ratio = number of ED visits/10,000 prescriptions
… confidence intervals are not provided, if RSE is greater than 50
** confidence intervals could not be obtained, estimates are considered to be imprecise
Source: IMS Health: Vector One ® National, Extracted 7/09 and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

Table 3.2 shows the national estimates of Adverse Reaction ED visits associated with analgesic and respiratory hydrocodone containing products as well as "abuse ratios' for each category. There were 26,756 ED visits in 2004. The number increased to 64,779 visits (142%) in 2007 for analgesic hydrocodone products. The number of Adverse Reaction ED visits associated with respiratory hydrocodone products ranged from 2,086 ED visits in 2004 and1,831 ED visits in 2007 and varied inconsistently by year. It is important to note, that the RSE for the estimates in 2004 – 2006 for the hydrocodone

respiratory products were too large to produce confidence intervals and the estimates themselves cannot be regarded as precise ones.

The adverse reaction ratios, for analgesic hydrocodone products were 2.4 ED visits per 10,000 prescriptions in 2004 and increased to 4.9 ED visits per 10,000 prescriptions in 2007 (104%). For respiratory hydrocodone products, the ratios ranged irregularly over the four years from a low of 1.7 in 2005 to a high of 2.2 in 2004 visits per 10,000 prescriptions.

Table 3.2: National Estimates of Adverse Reaction ED Visits Reported in DAWN and Number of Adverse Reaction ED Visits per 10,000 Prescriptions for Analgesic and Respiratory Hydrocodone Containing Products -- 2004 - 2007

Total Adverse Reaction ED Visits	***2004+***	***2005***	***2006***	***2007***
Analgesic and Respiratory Products	26,756	44,221	54,533	64,779
Confidence Intervals	(17,141, 36,370)	(32,363, 56079)	(41,806, 67,260)	(47,688, 81,869)
Analgesic combinations	24,670	42,258	52,307	62,948
Confidence Intervals	(16,387, 32,952)	(31,040, 53,475)	(40,457, 64,156)	(46,527, 79,368)
Respiratory combination**	2,086	1,963	2,226	1,831
Confidence Intervals	...	...	...	...
Hydrocodone Prescriptions				
TOTAL Hydrocodone Market	**109,738,552**	**120,091,780**	**126,492,450**	**133,228,908**
Analgesic Products	100,322,326	108,207,757	115,680,718	122,929,534
Respiratory Products	9,416,226	11,884,023	10,811,732	10,299,374
Adverse Reaction Ratios*				
Both Analgesic and Respiratory Products	**2.4**	**3.7**	**4.3**	**4.9**
Analgesic Products	2.5	3.9	4.5	5.1
Respiratory Products	2.2	1.7	2.1	1.8

*adverse reaction ratio = number of ED visits/10,000 prescriptions
… confidence intervals are not provided, if RSE is greater than 50
** confidence intervals could not be obtained, estimates are considered to be imprecise
+ difference in the number of adverse reactions reported from 2004 to other years are the result of training of medical extractors
Source: IMS Health: Vector One ® National, Extracted 7/09 and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

Table 3.3 is a summary the number of non-medical AllMA ED visits per Adverse Reaction ED visits for analgesic and respiratory hydrocodone containing products for the years 2004 -2007. Except for 2004, the ratio of AllMA (abuse/misuse) visits per Adverse Reaction visits remained relatively constant over time.

Finally, there were approximately 1.3 NMUP visits per adverse reaction case for analgesic hydrocodone products and 0.3 NMUP visits per adverse reaction case for respiratory hydrocodone products.

Table 3.3: National Estimates of All Medical Abuse (AllMA) and Adverse Reaction ED Visits Reported in DAWN and All Non-Medical Use ED Visits per Adverse Reaction ED Visits for Analgesic and Respiratory Hydrocodone Containing Products -- 2004 -2007

AllMA ED Visits	***2004***	***2005***	***2006***	***2007***
Analgesic and Respiratory Products	**46,924**	**56,037**	**67,043**	**77,560**
Analgesic Hydrocodone/combinations	46,535	55,704	66,114	76,945
ED visits -- Respiratory Hydrocodone /combinations	*389*	*333*	*929*	616
Adverse Reactions ED Visits[+]				
Analgesic and Respiratory Products	**26,756**	**44,221**	**54,533**	**64,779**
Analgesic Hydrocodone/combinations	24,670	42,258	52,307	62,948
ED visits -- Respiratory Hydrocodone /combination**	2,086	1,963	2,226	1,831
AllMA ED Visits per Adverse Reaction ED Visits				
Analgesic and Respiratory Products	**1.8**	**1.3**	**1.2**	**1.2**
Analgesic Hydrocodone/combinations	1.9	1.3	1.3	1.2
ED visits -- Respiratory Hydrocodone /combination**	0.2	0.2	0.4	0.3

*adverse reaction ratio = number of ED visits/10,000 prescriptions
[+] difference in the number of adverse reactions reported from 2004 to other years are the result of training of ED reporters
Source: IMS Health: Vector One ® National, Extracted 7/09 and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

4 DISCUSSION

As can be seen in Table 1, the number of AllMA ED visits and adverse reaction ED visits associated with analgesic hydrocodone products is large compared to the number of ED visits associated with respiratory hydrocodone products and increases over time. However, after adjusting for drug utilization these differences attenuate for adverse reaction ED visits and, although lower, the increase over time remains for AllMA visits.

It is important to note the following limitations of this analysis. The estimates provided are not true ratios or rates. Each dataset (DAWN and IMS VONA) has different sampling methodologies, different populations and different methods for calculating point estimates and respective confidence intervals. Furthermore, these data are not linked, that for each dataset, data is collected independently. The individuals who went to the emergency room may not have had a prescriptions for the drugs associated with the ED visit. Therefore, the observations are ecological associations only.

Another important limitation is that DAWN data represent patients that were able to make it to the emergency room. Any differential in the risk of death that occurs prior to the ED visits will not be captured using DAWN ED data. Conversely, it is also possible that abuse of these cough and cold products does not result in an ED visit. Lastly, this analysis provides one estimate that includes a variety of respiratory hydrocodone combinations and as a result, inferences between these products cannot be made.

5 CONCLUSIONS

There is limited evidence of drug abuse for respiratory hydrocodone products. The use of these products, however, is somewhat low and some misuse/abuse is still found in DAWN. Therefore, OSE/DEPI recommends to examine this issue further.

6 RECOMMENDATIONS

Based on the limited evidence found in DAWN, the abuse of respiratory hydrocodone products appears to be lower than for analgesic hydrocodone products. Given significantly lower rates of drug utilization and evidence that some albeit much lower, abuse ratios were found with these products, OSE/DEPI makes the following recommendations for additional studies:

1) Abuse liability studies should be required of the sponsors submitting NDA's
2) Conducting these studies post-approval is appropriate
3) Without more information on the different molecular entities, the studies should be conducted on all respiratory hydrocodone containing products

APPENDIX

IMS Vector One®: National (VONA)

The IMS, Vector One®: National (VONA) database 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 sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

Table A.1: Total Dispensed Prescriptions for Hydrocodone Products

Table 1. Total Dispensed Prescriptions for Hydrocodone Products through U.S. Outpatient Retail Pharmacies, 2004-2007

	2004		2005		2006		2007	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	*%*	N	*%*	N	*%*	N	*%*
TOTAL MARKET	**109,738,552**	***100.0%***	**120,091,780**	***100.0%***	**126,492,450**	***100.0%***	**133,228,908**	***100.0%***
Hydrocodone Analgesic Products	100,322,326	*91.4%*	108,207,757	*90.1%*	115,680,718	*91.5%*	122,929,534	*92.3%*
Hydrocodone Cough and Cold Products	9,416,226	*8.6%*	11,884,023	*9.9%*	10,811,732	*8.5%*	10,299,374	*7.7%*

Source: MS Vector One®: National. Data Extracted 7-6-09. File: VONA 2009-1034 TRx 7-6-09.xls

Table A.2: List of Analgesic and Respiratory Hydrocodone Products

Drug ID	*Drugs of interest*	*Category*
d03075	hydrocodone	CNS
d03428	acetaminophen-hydrocodone	CNS
d03429	aspirin-hydrocodone	CNS
d04225	hydrocodone-ibuprofen	CNS
d03352	hydrocodone-pseudoephedrine	Respiratory
d03353	hydrocodone-phenylpropanolamine	Respiratory
d03366	hydrocodone/phenylephrine/pyrilamine	Respiratory
d03375	hydrocodone/pheniramine/PE/PPA/pyrilamine	Respiratory
d03915	hydrocodone-potassium guaiacolsulfonate	Respiratory
d04152	hydrocodone-phenylephrine	Respiratory
d04350	hydrocodone/potassium guaiacolsulfonate/PSE	Respiratory
d06669	hydrocodone/pseudoephedrine/triprolidine	Respiratory
d05426	brompheniramine/hydrocodone/phenylephrine	Respiratory
d04880	brompheniramine/hydrocodone/pseudoephedrine	Respiratory
d07067	chlorpheniramine/guaifenesin/hydrocodone/PSE	Respiratory
d03361	chlorpheniramine/hydrocodone/phenylephrine	Respiratory
d03416	chlorpheniramine/hydrocodone/PSE	Respiratory
d03356	chlorpheniramine-hydrocodone	Respiratory
d06058	dexbrompheniramine/hydrocodone/phenylephrine	Respiratory
d05365	dexchlorpheniramine/hydrocodone/phenylephrine	Respiratory
d04925	diphenhydramine/hydrocodone/phenylephrine	Respiratory
d03420	guaifenesin/hydrocodon/pheniram/PPA/pyrilamin	Respiratory
d03414	guaifenesin/hydrocodone/pheniramine/PE/PPA	Respiratory
d03403	guaifenesin/hydrocodone/phenylephrine	Respiratory
d03404	guaifenesin/hydrocodone/pseudoephedrine	Respiratory
d03396	guaifenesin-hydrocodone	Respiratory

Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

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:	2/9/2011
To:	Michael Klein, PhD, Director Controlled Substance Staff Office of the Center Director
Through:	Judy A. Staffa, Ph.D., R.Ph, Acting Deputy Director Division of Epidemiology Office of Surveillance and Epidemiology
From:	Catherine Dormitzer Ph.D., MPH, Pharmacoepidemiologist Julia Ju, PharmD., PhD., Pharmacoepidemiologist Hina Mehta, PharmD., Drug Utilization Analyst Amarilys Vega, MD, MPH, Medical Officer Division of Epidemiology Office of Surveillance and Epidemiology
Subject:	Evaluation of the validity of the epidemiological methods and approaches that were used in the DEA's petition for rescheduling hydrocodone combination products from Schedule III to II
Drug Name(s):	Hydrocodone combination products
Submission Number:	
Application Type/Number:	
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EXECUTIVE SUMMARY

The Controlled Substance Staff (CSS) requested the Office of Surveillance and Epidemiology (OSE), Division of Epidemiology (DEPI), to review the reconsideration of a petition entitled "*Hydrocodone combination products: an eight-factor analysis*" submitted by the Drug Enforcement Agency (DEA) requesting to reschedule hydrocodone combination products from Schedule III to Schedule II. DEA considers that Schedule III controls for hydrocodone combination products are not adequate to protect public health because of the magnitude of abuse and diversion. The DEA's first request for rescheduling hydrocodone combination products (July 28, 2004), was not supported by the Department of Health and Human Services (DHHS). Analyses provided by epidemiologists in the Division of Drug Risk Evaluation (DDRE, DEPI's predecessor) were a part of the DHHS response to DEA. The petition for reconsideration document contained multiple data analyses with various data sources and provided national and regional estimates of the drug abuse-related health outcomes of hydrocodone combination products. The purpose of this review is to evaluate DEA's epidemiological methods and analyses included in the petition reconsideration document.

Summary of Findings

The validity of the inferences made by comparing *drug abuse-related health outcome rates* between two products relies on the adequacy of the comparator drug and the selection of a suitable denominator.

Selected Comparators

The DEA chose oxycodone products (Schedule II) as a comparator to hydrocodone combination products to evaluate the magnitude of abuse and diversion of hydrocodone combination products in the U.S.

The criteria for the selection of oxycodone as the comparator drug, oxycodone, is appropriate include the following:

1. Scheduling level: The comparator drug included is a level C-II .
2. Indication: The comparator drug is an oral opioid analgesics used for similar indications, namely moderate to severe pain relief.
3. Chemical Entity: The comparator drug is an opiate.
4. Approval date: Hydrocodone is a DESI drug that was subject to the pre-1962 (safety only) NDA process, therefore oxycodone with similar approval dates close to hydrocodone is appropriate.
5. High sales volume: Given the high sales volume of hydrocodone combination products, oxycodone has the next highest volume opioid analgesic..

DEPI agrees that the selection of oxycodone products as a comparator was a reasonable one.

Selected Denominators

Drug abuse-related health outcome rate estimates in the DHHS scheduling document employed *Total Number of Prescriptions* as the denominator. The use of a different set of denominators to estimate the rates of drug abuse-related health outcomes is at the crux of DEA's analyses of the data

included in their petition for reconsideration. The DEA stated that the validity of using the *Total Number of Prescriptions* to compare the availability of two or more drugs depends on how similar these products are in relation to: (1) average days of therapy per prescription, (2) composition type (single-entity vs. combination product), (3) total dosage unit per prescription, (4) potency-adjusted drug amounts per each dose unit, and (5) clinical indications. DEA concluded that due to significant differences between hydrocodone combination products and oxycodone products in these five elements, a comparison using *Total Number of Prescriptions* was not valid. Instead of using *Total Number of Prescriptions* as a denominator, DEA's analyses employed *Total Patient-days of Therapy*, and *Total Amount of Substance Distributed* (sales, in Kg) as denominators. DEPI agrees it is important to take the above 5 elements into consideration when comparing the risk profiles of two or more products, but does not support DEA's interpretation of some of their results.

DEPI reassessed the epidemiological methods employed by DDRE in their original response (review dated 1/7/2007) and considered DEA's new analytical methods as well as other approaches.

Based on this evaluation, DEPI determined that the assessment of the abuse and misuse of a drug product must include analyses of ***patient exposure-based risk profile*** and ***population exposure-based risk profile***. DEA did not consider these concepts and the differences between these analyses.

In a 2007 publication, Smith et al[1] concluded that, *"Population- and patient based rates are complementary tools that address different public health questions. Population-based rates describe the health-related burden of nonmedical opioid analgesic use on the community as a whole, while patient-based rates show this burden ("risk") in relation to the level of corresponding medicinal use ("benefit") within a given area".*

These different types of rates provide important metrics to consider in the evaluation of the public health impact of hydrocodone combination products. In addition, characterization of a product's risk profile is required to inform the drug scheduling process. Patient exposure-based denominators considered by DEPI in this review included *Total Number of Prescriptions*, *Total Patient-days of Therapy*, *Total Number of Extended Units,* and *Total Number of Patients*. Population exposure-based denominators included the *General Population* (census data) and/or *Total Amount of Substance Distributed* (in kilograms). Population exposure-based rates provide a way to assess a product's abuse/misuse risk profile from a community perspective while patient exposure-based rates provide a metric to assess the abuse/misuse risk from a patient's perspective.

Although each dataset evaluated had the ability to compute confidence intervals, the sources for numerators and denominators are derived using different sampling methodologies and populations, thus, confidence intervals on rates of drug abuse-related health outcomes cannot be computed. Of the patient exposure-based denominators assessed in this review, drug abuse-related health outcome rate estimates using *Extended Units* dispensed as a denominator provided the best metric of patient exposure-based risk (this denominator accounts for the variability in days of therapy and dosage units per prescription), while *Total Amount of Substance Distributed* likely provided the best metric of population exposure-based risk (however, this denominator does <u>not</u> account for the variability in all five elements listed above).

Drug Abuse-Related Health Outcome Rates Analyses

The data sources used in DEA's analyses included the National Poison Data System (NPDS, 2002-2006), Drug Abuse Warning Network (DAWN, 1994-2002, and 2004-2006), Florida Department of Law Enforcement (FDLE) medical examiner data (2005-2007), National Survey on Drug Use and Health (NSDUH, 2002-2005), and Monitoring the Future (MTF, 2002-2007). Although it is appropriate to use *Total Patient-days of Therapy*, and *Total Amount of Substance Distributed* to estimate the rate of abuse-related health outcomes, the results of DEA's analyses do not fully support their conclusion that hydrocodone combination products have a potential for abuse similar to oxycodone products controlled in schedule II. DEA's conclusions were primarily based on rates calculated using *Total Amount of Substance Distributed* as the denominator.

DEPI analyses showed that rates of drug abuse-related health outcomes calculated using outcome data from NPDS, DAWN, and FDLE medical examiner and a patient exposure-based denominator were higher for oxycodone products. However, similarly calculated rates using NSDUH data were slightly lower for oxycodone products when compared to hydrocodone combination products. Regarding drug abuse-related health outcomes, DEPI concluded that the preponderance of the data suggested that hydrocodone combination products have a more favorable risk profile (i.e., less abuse potential) than oxycodone products. Conversely, data from NPDS, DAWN, FDLE medical examiner, NSDUH, and MTF demonstrated a significant burden to the community due to the abuse/misuse of hydrocodone combination products, likely due to the greater number of prescriptions for hydrocodone combination products and therefore its increased availability in the community.

Analyses comparing oxycodone and tramadol single ingredient vs. combination products demonstrated that combination products have lower rates of Emergency Department mentions than single ingredient products. These findings could be attributed to the lower amount of opiate contained in combination products, to the addition of other products such as acetaminophen, or due to a combination of both factors. DEPI concluded that the data assessed in this review do not support DEA's theory that nonnarcotic active ingredients (acetaminophen, ibuprofen, aspirin, chlorpheniramine, or homatropine) present in hydrocodone combination products do not reduce the abuse potential of hydrocodone.

A major limitation of these analyses is the inability to calculate confidence intervals around estimates, which limits our ability to make statistical comparisons between hydrocodone products and oxycodone products. Given the relatively small numerator counts and large denominators, it is possible that confidence intervals, if calculable, would be large and may overlap – prohibiting discrimination between outcome rates for these two products. However, this cannot be known for certain and we are left with only the ability to informally compare rates, which we have done to the best of our ability in this review.

Conclusions

- The assessment of the abuse and misuse of hydrocodone combination products must include both analyses of the population exposure-based risk profile and the patient exposure-based risk profile.
- The selection of oxycodone products as a comparator to hydrocodone combination products is reasonable.

- Population exposure-based and patient exposure-based drug abuse-related health outcome rates are important metrics to consider in the evaluation of the public health impact and risk profile of hydrocodone combination products.
- Population -exposure based rates provide a way to assess a product's abuse/misuse risk profile from a community perspective while patient exposure-based rates provide a metric to assess the abuse/misuse risk from a patient's perspective.
- Of the patient exposure-based denominators assessed in this review, drug abuse-related health outcomes rate estimates using *Extended Units* dispensed as a denominator likely provided the best metric of patient exposure-based risk, while *Total Amount of Substance Distributed* likely provided the best metric of population exposure-based risk.
- The preponderance of the data evaluated in this review indicated that, in spite of the significantly larger volume of prescriptions of hydrocodone combination products, these products appear to have a lower risk profile than oxycodone products. However, these data also suggested that the abuse/misuse of hydrocodone combination products may represent a significant risk to the community.
- DEA's asserts a theory that the abuse potential of hydrocodone products are not reduced by the presence of nonnarcotic active ingredients (acetaminophen, ibuprofen, aspirin, chlorpheniramine, or homatropine) present in hydrocodone combination products. The data analyzed in this review do not support this theory.

1 BACKGROUND/HISTORY

A petition was submitted to the Drug Enforcement Administration (DEA) by a practicing physician specializing in addiction medicine requesting hydrocodone combination products be rescheduled from Schedule III to Schedule II based on the Controlled Substances Act (CSA) in January 1999. Accordingly, the DEA submitted a request to the Department of Health and Human Services (DHHS) for a scientific evaluation and rescheduling recommendation on hydrocodone combination products on July 28, 2004. On March 6, 2008, DHHS responded with a recommendation that hydrocodone combination products remain under Schedule III. However, the DEA considered that Schedule III controls for hydrocodone combination products were not adequate to protect public health because of the magnitude of abuse and diversion.

The DEA collected and reanalyzed new data regarding the abuse and diversion of hydrocodone products since then and on Feb 13, 2009, submitted a new request to FDA for a scientific and medical evaluation and scheduling recommendation based on the new data. The petition reconsideration document is entitled "*Hydrocodone combination products: an eight-factor analysis*" and contained multiple data analyses with various data sources and provided national and regional estimates of the drug abuse-related health outcomes of hydrocodone combination products. The Controlled Substance Staff (CSS) requested the Office of Surveillance and Epidemiology (OSE), Division of Epidemiology (DEPI), to review the petition reconsideration document. Analyses provided by epidemiologists in the Division of Drug Risk Evaluation (DDRE, DEPI's predecessor) were a part of the DHHS original response to DEA. The purpose of this review is to evaluate DEA's epidemiological methods and analyses.

2 REVIEW METHODS AND MATERIALS

The DEA's petition titled "*Hydrocodone combination products: an eight-factor analysis*". The eight factors specified in 21 U.S.C. 811 (c) include: 1) its actual or relative potential for abuse; 2) scientific evidence of its pharmacological effects, 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, risks are there to the public health; 7) its psychic or physiological dependence liability; and 8) whether the substance is an immediate precursor of a substance already controlled under this subchapter. This review focused on the epidemiological approach used by DEA to assess abuse liability of hydrocodone products and its comparator drug oxycodone. DEPI reassessed the epidemiological methods employed by DDRE in their original response (review dated 1/7/2007) and considered DEA's new analytical methods as well as other approaches.

3 EVALUATION OF DEA REPORT

3.1 STUDY OBJECTIVES

3.1.1 Study Objective

The objective of the eight factor analysis by DEA is to provide scientific and medical evidence of the abuse and diversion of hydrocodone combination products to support the rescheduling recommendation from schedule III to schedule II.

3.1.2 DEPI Comments on Study Objective

DEA is considering drug abuse events in the context of drug exposure opportunities and DEPI agrees that this epidemiological approach is appropriate.

3.2 STUDY COMPARATORS

The following sections present DEA's rationale for the selection of a comparator drug and DEPI reviewers' comments.

3.2.1 Proposed Comparators

The objective of the eight factor analyses is to provide scientific and medical evidence of the abuse and diversion of hydrocodone combination products to support the rescheduling recommendation from Schedule III to Schedule II. The DEA chose oxycodone products (Schedule II) as a comparator to hydrocodone combination products to evaluate the magnitude of diversion and abuse of hydrocodone combination products in the U.S. The reasons provided for DEA's selection of oxycodone products as the comparator included:

(1) both hydrocodone and oxycodone are high-efficacy μ-opioid receptor agonists

(2) both single ingredient products are scheduled II substances under CSA

(3) the analgesic effect of hydrocodone bitartrate is equipotent to oxycodone hydrochloride on a milligram basis as an oral analgesic

(4) hydrocodone bitartrate is approximately equipotent or slightly less potent than oxycodone hydrochloride on a milligram basis in its abuse liability

(5) about 90% of both hydrocodone and oxycodone combination products contain acetaminophen (according to prescription data from IMS Health)

DEA agrees that the best comparator for this analysis on the diversion and abuse of hydrocodone products are oxycodone products

Unlike hydrocodone which was dispensed nearly 100% in combination products in 2007 (Section 1.2.2.1. on page 15 of the DEA report), oxycodone was dispensed as both single ingredient (31% of

total number of prescriptions and 73% of the total amount distributed in Kg) and combination products (about 69% of total number of prescriptions and 27% of total amount distributed in Kg). See **Table 1** Percentage of the *Total Number of Prescriptions* and *Total Amount of Substance Distributed* (sales in kg) for Hydrocodone and Oxycodone Containing Products in 2007 below.

Table 1 Percentage of the *Total Number of Prescriptions* and *Total Amount of Substance Distributed* (sales in kg) for Hydrocodone and Oxycodone Containing Products in 2007 *

Product Name	% Total Number of Prescriptions	*% Total Amount Distributed*
HYDROCODONE		
o Single ingredient	<1	*<1*
o Combination	~100	*~100*
OXYCODONE		
o Single ingredient	31	*73*
• *Immediate release*	*13*	-
• *Extended release*	*18*	-
o Combination	69	27

** Data obtained from DEA Report: IMS Health, IMS National Sales Perspectives (January 2002-December 2007, Retail Channels, Data Extracted September 2008.*

DEA also considered the use of propoxyphene (Scheduled IV) and codeine (Scheduled III/IV) as reference comparator drugs. DEA stated in their report that these two drugs were not suitable comparators due to the limited data available on these two drugs.

Codeine combination products are classified as Schedule III, while codeine single ingredient drugs are classified as Schedule II (similar to hydrocodone combination and single ingredient products). However, as stated in the DEA report, there are limitations associated with the use of codeine combination products as a comparator. One of the limitations is related to the use of codeine in non-analgesic products, such as cough syrups that are available over-the-counter while hydrocodone combination products are not. Additionally, few databases contain drug abuse-related health outcomes (numerator) data on codeine combination products.

3.2.2 DEPI Comments on Proposed Comparators

The use of oxycodone products as a comparator to evaluate the magnitude of abuse and diversion of hydrocodone combination products is acceptable for these analyses. Like hydrocodone, oxycodone is a widely used opioid analgesic product that has been on the market for almost the same amount of time as hydrocodone.

Although, additional Schedule III comparator products would be useful to examine whether hydrocodone combination products (Schedule III) have higher rates of abuse and diversion than other Schedule III products, there are no appropriate comparator opioid analgesic products currently marketed.

3.3 STUDY OUTCOMES

The outcome measures for drug abuse/misuse tend to be non-specific and potential misclassification bias may easily be introduced. Furthermore, the study outcomes may be underestimated due to

under-reporting given that most of the data is self-reported. However, the magnitude of potential bias introduced by differences in underreporting between hydrocodone combination products and oxycodone products is unknown.

3.4 DENOMINATORS FOR CALCULATING ABUSE RATES

3.4.1 Denominators-Assessment by DEA

The epidemiological analyses conducted by DEA considered drug abuse-related health outcomes (numerator) in the context of drug exposure or availability in the community (denominator).

DEA's analyses used two different denominators: *Total Patient-days of Therapy* and *Total Amount of Substance Distributed*. Following is a summary of DEA's rationale for using the two new denominators rather than the *Total Number of Prescriptions*, which was used in previous analyses.

Total Number of Prescriptions

DEA report states that the validity of using the *Total Number of Prescriptions* as a denominator to compare the availability of two or more drugs depends on how similar these products are in relation to: (1) average days of therapy per prescription, (2) composition type (single-entity vs. combination product), (3) total dosage units per prescription, (4) potency-adjusted drug amounts per each dose unit, and (5) clinical indications.

The DEA reported that a comparison between hydrocodone and oxycodone is hindered by significant differences in the five factors listed above.

- Average days of therapy per prescription – The number of days of therapy per prescription is not taken into consideration when employing the total number of prescriptions as a denominator.
- Composition type (single-entity vs. combination product) – See section **3.2.2, Table 1** Percentage of the *Total Number of Prescriptions* and *Total Amount of Substance Distributed* (sales in kg) for Hydrocodone and Oxycodone Containing Products in 2007 above.
- Total dosage unit per prescription – The total number of prescriptions of hydrocodone products is much larger than the number of prescriptions for oxycodone products. The average number of dosage units per hydrocodone prescription is similar to that of oxycodone combination products. However, the average number of dosage units of single-entity oxycodone extended and immediate release is larger than the number of dosage units per prescription of hydrocodone and oxycodone combination products (3.5-4 fold larger). (See Tables 2 and 3 DEA report.)
- Potency-adjusted drug amounts per each dose unit – The total number of dosage units of hydrocodone distributed annually is about twice that of oxycodone. However, the average drug amount (in mg) per each dosage unit of oxycodone single ingredient is significantly higher than the drug amount found in oxycodone combination products and hydrocodone combination products. (See Table 3 in the DEA report.)
- Clinical indications – No comments included in the DEA report.

Total Patient-days of Therapy

DEA expanded the DHHS analysis by using *Total Patient-days of Therapy* as a denominator. *Total Patient-days of Therapy* is defined as the total number of days for which annual prescriptions for a given opioid drug are expected to provide treatment for all the patients who are prescribed the same opioid drug. It is calculated by multiplying the total number of prescriptions by the average days of

therapy per prescription. The *Total Patient-days of Therapy* are significantly higher for hydrocodone products than for oxycodone. (See Table 4 in the DEA report.)

Total Amount of Substance Distributed (sales in Kg)

DEA also used *Total Amount of Substance Distributed* in salt form as a denominator for calculating drug abuse-related health outcome rates. These data came from the Automation of Reports and Consolidated Orders System (ARCOS) database. The total consumption of hydrocodone bitartrate salt (kg) was estimated by using the weight of total hydrocodone base divided by its proportion of molecular weight of base in hydrocodone bitartrate salt. The total consumption of oxycodone hydrochloride salt (kg) was calculated by using the oxycodone base weight divided by its proportion of molecular weight of base in oxycodone hydrochloride salt. DEA's rationale for utilizing this denominator was: (1) to test the theory that the nonnarcotic active ingredients (acetaminophen, ibuprofen, aspirin, chlorpheniramine, or homatropine) present in hydrocodone combination products reduce the abuse potential of hydrocodone and (2) this denominator eliminates variability related to drug-specific differences such as product composition, formulation, total dosage units per prescription, and drug amounts per dosage unit. DEA stated in their report that there is no evidence that hydrocodone and oxycodone are clandestinely produced in the US or are illicitly obtained from foreign sources. In addition, in contrast to commercially available prescription databases, the ARCOS database accounts for drug amounts that are diverted from pharmacies, hospitals, and physicians' offices.

3.4.2 DEPI Comments Regarding Denominators

Often, drug abuse-related health outcome rates are employed to compare two or more drug products. The validity of the inferences made by comparing the rates between two products relies on the adequacy of the selected comparator drug and on the selection of a suitable denominator. Potential denominators used to calculate drug abuse-related health outcome rates include: (1) the general population (census data), (2) total amount of substance distributed, (3) total number of prescriptions, (4) total number of patient-days of therapy, (5) total number of extended units dispensed (number of pills contained in each prescription), and (6) total number of patients receiving a prescription. Estimates using the general population and estimates using total amount of drug distributed as denominators generate *population exposure based rates*; estimates using total number of prescriptions, total number of patient-days of therapy, total number of extended units dispensed, and total number of patients dispensed prescriptions produce *patient exposure-based rates*. Population exposure-based rates provide a way to assess a product's abuse/misuse risk profile from a community perspective while patient exposure-based rates provide a metric to assess the abuse/misuse risk from a patient's perspective.

In a 2007 publication, Smith et al discussed the value of abuse-related health outcome rate estimates in inter- and intra-drug comparisons of abuse patterns and in the assessment of the risk-benefit profile of a drug or group of drugs. The authors stated that using census data as denominator (surrogate for the exposed or at risk population) generated a *population-based rate*, a public health metric that is comparable to other public health metrics. Use of *patient-based denominators* (derived from drug utilization data) to estimate the rate of the number of persons receiving a prescription to the number of individuals abusing the product provide a metric of the drug's *risk-benefit profile*. Smith et al concluded that, *"Population- and patient based rates are*

complementary tools that address different public health questions. Population-based rates describe the health-related burden of nonmedical opioid analgesic use on the community as a whole, while patient-based rates show this burden ("risk") in relation to the level of corresponding medicinal use ("benefit") within a given area".

DEA made no distinction between **population** exposure-based risk profile and **patient** exposure-based risk profile in their report.

A comparison of the abuse potential between hydrocodone combination products and oxycodone products must take into account differences in (1) average days of therapy per prescription, (2) composition type (single-entity vs. combination product), (3) total dosage units per prescription, (4) potency-adjusted drug amounts per each dose unit, and (5) clinical indications. In this case, drug abuse-related rates calculated employing a numerator and a denominator that cannot minimize these differences will not provide a precise characterization of the risk profile for individuals who have exposure to the prescriptions. Given the limitations imposed by the available numerator data, calculation of drug abuse-related health outcome rates using prescription-based denominators, including a simultaneous adjustment for the 5 elements mentioned above, is not feasible.

Table 2 Characteristics of Drug Abuse-Related Health Outcome Measures

Characteristics	Population Exposure-Based Rates [+]		*Patient Exposure-Based Rates*			
	Denominators		Denominators			
	General population[*]	Amount of drug sales in kg. distributed[**]	Total number of Rxs[***]	Total number of patient-days of therapy[***]	Total number of extended units (pills) dispensed[^]	*Total number of patients receiving a Rx* [&]
Characterizes the risk due to abuse/misuse[+]						
o *from a community perspective (population exposure-based risk profile)*	*Yes*	*Yes*	*No*	*No*	*No*	No
o *from a patient's perspective (patient exposure-based risk profile)*	*No*	*No*	*Yes*	*Yes*	*Yes*	Yes
Accounts for variability in						
o *Dosage units per prescription*	*No*	*No*	*No*	*No*	*Yes*	No
o *Potency-adjusted drug amounts per each dose unit*	*No*	*No*	*Yes*[ii]	*Yes*[ii]	*Yes*[ii]	Yes[ii]
o *Average days of therapy per prescription*	*No*	*No*	*No*	*Yes*	*Yes*	No
o *Composition type (single-entity vs. combination product)*	*No*	*No*	*Yes*[ii]	*Yes*[ii]	*Yes*[ii]	Yes[ii]
o *Clinical indications*	*No*	*No*	*Yes*[ii]	*Yes*[ii]	*Yes*[ii]	Yes[ii]
Accounts for drug lost from the supply chain prior to prescription	No	Yes	No	No	No	No

[*] *Based on US census data;* [**]*Drug sales to the US population (in kilograms), based on data from the Automation of Reports and Consolidated Orders System (ARCOS);* [***]*Source: SDI: Vector One®: National. Extracted 1/11.;* [^] *Source: SDI: Vector One®: National. Extracted 1/11;* [&]*Source: SDI: Vector One®: Total Patient Tracker. Extracted 1/11.* [ii] *In the case of hydrocodone and oxycodone products, the limitations imposed by the nature of the available numerator data (i.e., data is not product specific and exposure information lack sufficient details), this denominator cannot be used to adjust for this factor.*
[+]*Population -exposure based provide a way to assess a product's abuse/misuse risk profile from a community perspective while patient exposure-based rates provide a metric to assess the abuse/misuse risk from a patient's perspective.*

Total Number of Prescriptions

This denominator is obtained from drug utilization databases (See **Appendix Table 1**). DEPI concurs with DEA that the significant differences between hydrocodone combination products and oxycodone products must be taken into consideration when selecting a suitable denominator for calculating rates of drug abuse-related health outcomes. A comparison of the abuse potential between hydrocodone combination products and oxycodone products must take into account differences in (1) average days of therapy per prescription, (2) composition type (single-entity vs. combination product), (3) total dosage units per prescription, (4) potency-adjusted drug amounts per each dose unit, and (5) clinical indications.

This denominator does not account for the variability between hydrocodone and oxycodone in dosage units per prescription and average days of therapy. If the cases of abuse (numerator) could be further characterized by potency, composition type, and clinical indications, it would be possible to adjust for the variability attributed to these factors. Due to these differences, the drug abuse-related health outcome rates calculated using this denominator will not provide a precise characterization of a drug's abuse/misuse risk profile. This denominator cannot measure the exposure to drugs that were diverted from pharmacies, hospitals, and physicians' offices, nor does it capture drug lost from the supply chain prior to prescription, in transit and at the wholesalers.

Total Patient-days of Therapy

This denominator is also obtained from drug utilization databases (See **Appendix Table 2 and 3**). . These data were obtained directly from the data vendor instead of multiplying the total number of prescriptions by the average days of therapy as computed by DEA. According to the data vendor, DEA's method will generate numbers that are close, but it does not take into account the different strengths/forms of a product. Within the context of this analysis, the use of the *Total Patient-days of Therapy* as a denominator provides a more refined metric of drug availability when compared to *Total Number of Prescriptions,* given that it accounts for the variability introduced by differences in the average days of therapy per prescription. If the cases of abuse (numerator) could be further characterized by potency, composition type, and clinical indications, it would be possible to use this denominator to adjust for the variability attributed to these factors.

DEPI examined its own data on the total number of prescriptions, total days of therapy, and mean days of therapy using SDI Vector One®: National data. In 1998, there were more than 62 million prescriptions dispensed for hydrocodone versus almost 16 million prescriptions dispensed for oxycodone and that number rose to almost 124 million and more than 49 million prescriptions dispensed in 2009 for hydrocodone and oxycodone, respectively. The average number of days of therapy for hydrocodone combination products was 14.4 whereas the average number of days of therapy for oxycodone products was 17.9 for the total market during year 2009. Average days of therapy ranged from 14.3 days of therapy for immediate release combination products to 27.5 days for extended release single ingredient products. (See **Appendix Table 2 and 3**).

This denominator cannot measure the exposure to drugs that were diverted from pharmacies, hospitals, and physicians' offices, nor does it capture drug lost from the supply chain prior to prescription, in transit and at the wholesalers.

Total Number of Extended Units Dispensed

DEA did not use this denominator in their analyses. Each "extended unit" or pill is an "exposure opportunity" and represents drug availability for abuse. The *Total Number of Extended Units* is

obtained from drug utilization databases and it represents the number of units (tablets, ml's, etc.) dispensed for a product for a given period of time. The total number of Extended Units for hydrocodone combination products is substantially higher than that of oxycodone products. (See **Appendix Table 4**)

Drug abuse-related health outcome rates calculated using this denominator account for the variability due to total dosage units per prescription (i.e., total number of pills) and due to the total days of therapy, thus providing a more refined estimate than the other prescription-based denominators previously discussed. For example, oxycodone extended release products are normally prescribed 1 pill every 12 hours, hydrocodone combination products, on the other hand, may be prescribed 2 pills every 6 hours, or 8 pills a day. Like with *Total Number of Prescriptions* and *Total Patient-days of Therapy,* if the cases of abuse (numerator) could be further characterized by potency, composition type, and clinical indications, it would be possible to use this denominator to adjust for the variability attributed to these factors.

This denominator cannot measure the exposure to drugs that were diverted from pharmacies, hospitals, and physicians' offices, nor does it capture drug lost from the supply chain prior to prescription, in transit and at the wholesalers.

Total Number of Patients

This denominator is also obtained from drug utilization databases and represents the total number of unique patients receiving a dispensed prescription for the product of interest See **Appendix Table 5.** DEA did not use this denominator in their analyses. *Total Number of Patients* could only account for drug-to-drug variability if the cases of abuse (numerator) could be further characterized by potency, composition type, and clinical indications. This denominator cannot measure the exposure to drugs that were diverted from pharmacies, hospitals, and physicians' offices, nor does it capture drug lost from the supply chain prior to prescription, in transit and at the wholesalers.

Total Amount of Substance Distributed (Kg)

The denominator *Total Amount of Substance Distributed* to the general US population is based on the total amount of hydrocodone bitartrate and oxycodone hydrochloride salts sold. This denominator accounts for all products sold annually regardless of the drug used medically or non-medically including the amounts of drug diverted from pharmacies, hospitals, and physicians' offices, or lost from the supply chain prior to prescription, in transit and at the wholesalers. However, drug abuse-related health outcome rate estimates based on this denominator must not be used to compare the risk of individuals who are exposed to hydrocodone combination products to the risk of oxycodone products because the amount of milligrams of opioid per pill is considerably lower for hydrocodone products than for oxycodone products. As mentioned above, each pill is an "exposure opportunity" or represents drug availability for abuse. DEPI conducted its own analysis by dividing the kilograms of opioid distributed that DEA provided in its report by the number of extended units dispensed for each drug product (extended units are the number of pills contained in each prescription). As **Table 3** presents the number of pills produced per kg for hydrocodone has remained fairly stable through time. It was 133,000 pills per kilogram in 1998 and 128,000 pills per kg in 2007. Oxycodone, however, had fewer pills produced per kg. In 1998 there were 99,000 pills dispensed per kg and that dropped to 66,000 pills dispensed in 2007.

Table 3 Number of Extended Units (pills) Dispensed per Annual Consumption of Drugs (in kg) from ARCOS, 1998-2007

Years	Hydrocodone Combination Products	Oxycodone Products
1998	133,926	99,101
1999	135,829	84,457
2000	134,731	68,794
2001	136,541	62,804
2002	125,683	62,190
2003	117,298	59,912
2004	121,127	60,614
2005	127,733	66,109
2006	126,776	66,043
2007	128,251	66,747

Source: SDI: Vector One®: National. Extracted 1/11; Annual Consumption of Drug in kg: DEA Report

The use of *Total Amount of Substance Distributed* to the population as a denominator does not account for the variability introduced by any of the five elements listed above and, to the contrary, eliminates all the variability between hydrocodone and oxycodone by assuming that all outcomes were the result of exposure to an equal amount of drug, preventing us from answering the question of whether the abuse potential differs between these products. Therefore, the use of this denominator cannot provide product-specific risk estimates. Instead, it provides a way to characterize the population exposure-based risk profile.

DEA used rates calculated using this denominator as evidence against the theory that the nonnarcotic active ingredients (acetaminophen, ibuprofen, aspirin, chlorpheniramine, or homatropine) present in hydrocodone combination products reduce the abuse potential of hydrocodone. However, to answer this question, the abuse rates of hydrocodone combination products should be compared with the rates of hydrocodone single ingredient products, which are not currently marketed. Therefore, this objective cannot be achieved.

General Population

This denominator is readily available from census data and when used for calculating rates of drug abuse-related health outcome it provides a good way to characterize the population exposure-based risk profile. Abuse rates calculated based on this denominator do not account for the variability due to differences between hydrocodone and oxycodone in average days of therapy per prescription, composition type (single-entity vs. combination product), total dosage units per prescription, potency-adjusted drug amounts per each dose unit, nor for clinical indications. Use of this denominator is based on the assumption that the whole population is at risk of exposure. This denominator cannot measure the exposure to drugs that were diverted from pharmacies, hospitals, and physicians' offices, nor does it capture drug lost from the supply chain prior to prescription, in transit and at the wholesalers.

In summary, population exposure-based, and patient exposure-based abuse/misuse rates are important metrics to consider in the evaluation of the public health impact of hydrocodone

combination products. Population exposure-based rate provide a way to assess a product's abuse/misuse risk profile from a community perspective while patient exposure-based rates provide a metric to assess the abuse/misuse risk from a patient's perspective.

3.5 DATA SOURCES

Two data sources were used in the DEA's analyses to estimate the denominator: IMS Health, National Prescription Audit (IMS NPA) Plus (2002-2007), and the Automation of Reports and Consolidated Orders System (ARCOS). The IMS NPA data measure the flow of prescriptions from pharmacies to patients in the U.S. The ARCOS data provide drug distribution data as an indicator of drug availability in the U.S. ARCOS is an automated, comprehensive drug reporting system that monitors the flow of DEA controlled substances from their point of manufacture through commercial distribution channels to point of sale or distribution at the dispensing level, hospitals, retail pharmacies, practitioners, and teaching institutions[2]. While NPA Plus data does not contain data from dispensing physicians, hospital pharmacies, clinic pharmacies, HMOs and home healthcare facilities, or drugs that are diverted from pharmacies, hospitals, and physician's offices, ARCOS data does account for this information.

Several analyses were conducted to estimate the drug-related morbidity and mortality due to abuse and misuse. The numerator data sources used included the National Poison Data System (NPDS) (2002-2006), Drug Abuse Warning Network (DAWN) (1994-2002, and 2004-2006), and Florida Department of Law Enforcement (FDLE) medical examiner data (2005-2007).

- The NPDS data, formerly known as Toxic Exposure Surveillance System (TESS), are compiled by the American Association of Poison Control Centers in cooperation with the majority of the poison centers in the U.S. NPDS is the only near real-time comprehensive poisoning surveillance database in the U.S. and holds more than 50 million poison exposure case records, with more than two million new records added each year.
- The DAWN data is a public health surveillance system that monitors selected, nationally representative, drug abuse related emergency department (ED) visits as well as deaths (mortality data are not nationally representative) investigated by medical examiners and coroners to track the impact of drug use, misuse, and abuse.
- The Florida Department of Law Enforcement (FDLE) medical examiner data contains information about the drug being the "cause" of death or merely present in the body at the time of death for deaths occurring in Florida.

Actual abuse data were obtained from two drug abuse surveys: the National Survey on Drug Use and Health (NSDUH) (2002-2005) and Monitoring the Future (MTF) (2002-2007).

- The NSDUH, formerly the National Household Survey on Drug Use (NHSDA), provides information on the prevalence, patterns, and consequences of the use and abuse of a number of illicit and prescription drugs in the general U. S. civilian non-institutionalized population, age 12 and older. This annual face-to-face survey provides national estimates of rates of use, numbers of users and other measures related to drugs, alcohol, and tobacco products.
- MTF is a questionnaire based survey of drug use among a representative sample of high school students in the U.S. MTF is an ongoing study funded by the National Institute on Drug Abuse.

Other data sources employed by DEA contain law enforcement information from spontaneous encounters as well as targeted, priority-based investigations, such as the National Forensic Laboratory Information System (NFLIS) and the System to Retrieve Information from Drug Evidence (STRIDE) data from the Office of Diversion Control, DEA. These data are from databases that are not public health surveillance systems and were not examined by DEPI.

DEPI agrees that the data sources used in the DEA's analyses are reasonable based on the limited availability of data to address this issue. The limitations associated with these data sources, however, should be considered in the regulatory decision making process. Also, DEPI conducted additional analyses which required drug utilization data from SDI, our current contractor for national-level prescription data. See the Appendix for a brief description of *SDI Vector One®: National (VONA) and SDI Vector One®: Total Patient Tracker (TPT)* databases**.**

3.6 DRUG ABUSE-RELATED HEALTH OUTCOMES DATA ANALYSES

3.6.1 National Poison Data System (NPDS)

3.6.1.1 DEA Analysis of NPDS Data

DEA examined the annual reports for the years 2002-2006 of NPDS data, for calls received by poison centers in the U.S that reported toxic exposures for hydrocodone and oxycodone products.

The number of toxic exposures (exposures that trigger calls to poison centers) for hydrocodone combination products were similar to those for oxycodone products from 2002 to 2006 using million *Total Patient-days of Therapy* as the denominator (see Figure 1 DEA report). Rates were between 20 and 25 exposures per million days of therapy for both hydrocodone and oxycodone products.

When *Total Amount of Substance Distributed* was used as the denominator however, the rates of toxic exposures per 100 kilograms of drug for hydrocodone combination products were higher than the corresponding rates for oxycodone products from 2002 through 2006 (see Figure 2 DEA report). It ranged from 55 to 45 exposures per 100 kilograms sold for hydrocodone products and 40 to 30 exposures per 100 kilograms sold for oxycodone. DEA also reported that the total annual fatalities involving exposure to hydrocodone combination products consistently exceeded those for oxycodone products (see Table 6 in DEA report).

3.6.1.2 DEPI Comments on DEA Analysis of NPDS Data

Although the total <u>number</u> of toxic exposures and fatalities reported by NPDS for hydrocodone combination products was higher than the corresponding numbers reported for oxycodone, note that the fatality <u>rate per thousand exposures</u> reported (calculated by DEPI and seen below in Table 4) was consistently lower for hydrocodone products.

Table 4 Fatality Rates Reported Among Cases of Toxic Exposure to Hydrocodone Combination Products and Oxycodone Products, National Poison Data System (NPDS) 2002-2006*

Year	Hydrocodone			Oxycodone		
	Toxic Exposures	Fatalities	Fatality Rate per 1,000 exposures	Toxic Exposures	Fatalities	Fatality Rate per 1,000 exposures
2002	17,429	66	3.79	10,515	63	5.99
2003	19,578	82	4.19	11,254	60	5.33
2004	22,654	86	3.80	12,603	61	4.84
2005	22,229	100	4.50	13,191	78	5.91
2006	22,244	105	4.72	13,473	91	6.75

**DEPI analysis. Source: National Poison Data System, 2002-2006*

DEPI recalculated the rates provided by DEA using *Total Patient-days of Therapy* and observed that Figure 1 in DEA report is not accurate. **Table 5** below presents the data used by DEA to estimate the rates of drug toxic exposures per million patient-days of therapy.

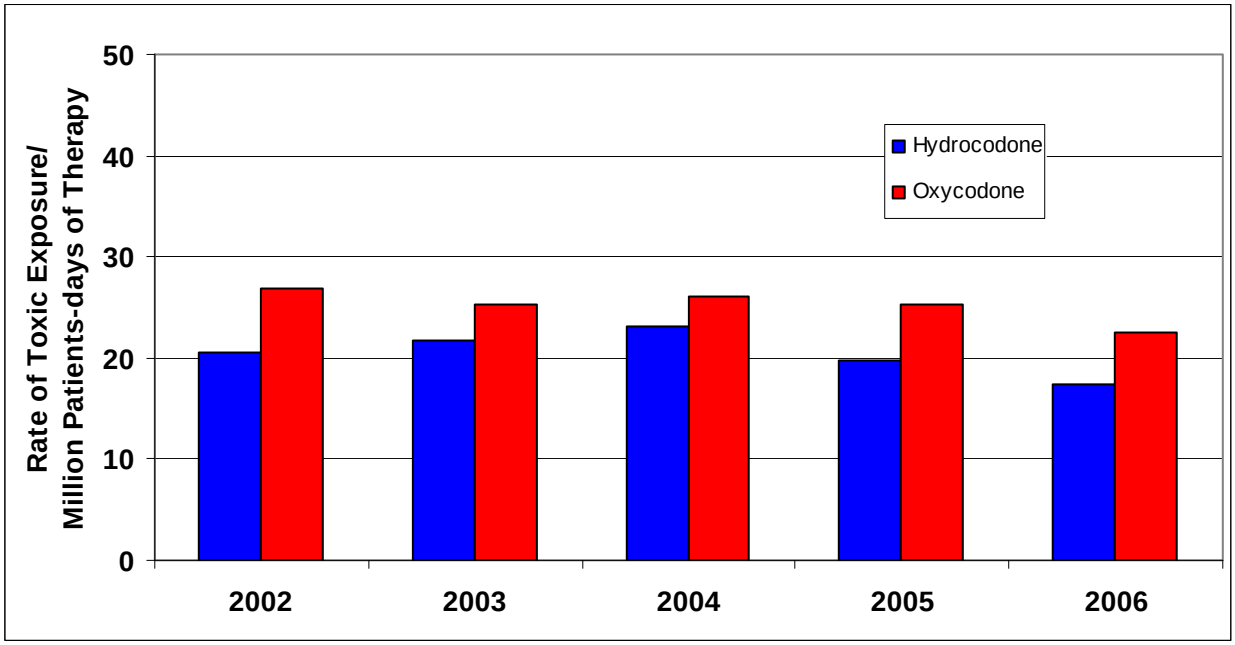
Table 5 Hydrocodone and Oxycodone Toxic Exposures per Million Patient-days of Therapy, NPDS 2002-2006*

Year	Hydrocodone			Oxycodone		
	Toxic Exposures	Patients-days of Therapy	Rate of Toxic Exposures per Million Patient-days of therapy	Toxic Exposures	Patients-days of Therapy	Rate of Toxic Exposures per Million Patient-days of therapy
2002	17,429	851,393,000	20.47	10515.00	391,543,000	26.86
2003	19,578	900,187,000	21.75	11254.00	445,639,000	25.25
2004	22,654	981,437,000	23.08	12603.00	483,288,000	26.08
2005	22,229	1,128,031,000	19.71	13191.00	521,955,000	25.27
2006	22,244	1,275,681,000	17.44	13473.00	600,291,000	22.44

**DEPI analysis using numbers from tables 4 and 6 in DEA report. Sources: NPDS and NPA Plus; * Total Number Patient-days of Therapy provided by DEA*

Figure 1 below (created by DEPI from data in Table 5 above) graphically depicts these rates using the same scale used by DEA in their Figure 1.

Figure 1 Hydrocodone and Oxycodone Toxic Exposures per Million Patient-days of Therapy, NPDS 2002-2006*



** DEPI analysis using data from Table 5 above. Source: Total Number Patient-days of Therapy provided by DEA.*

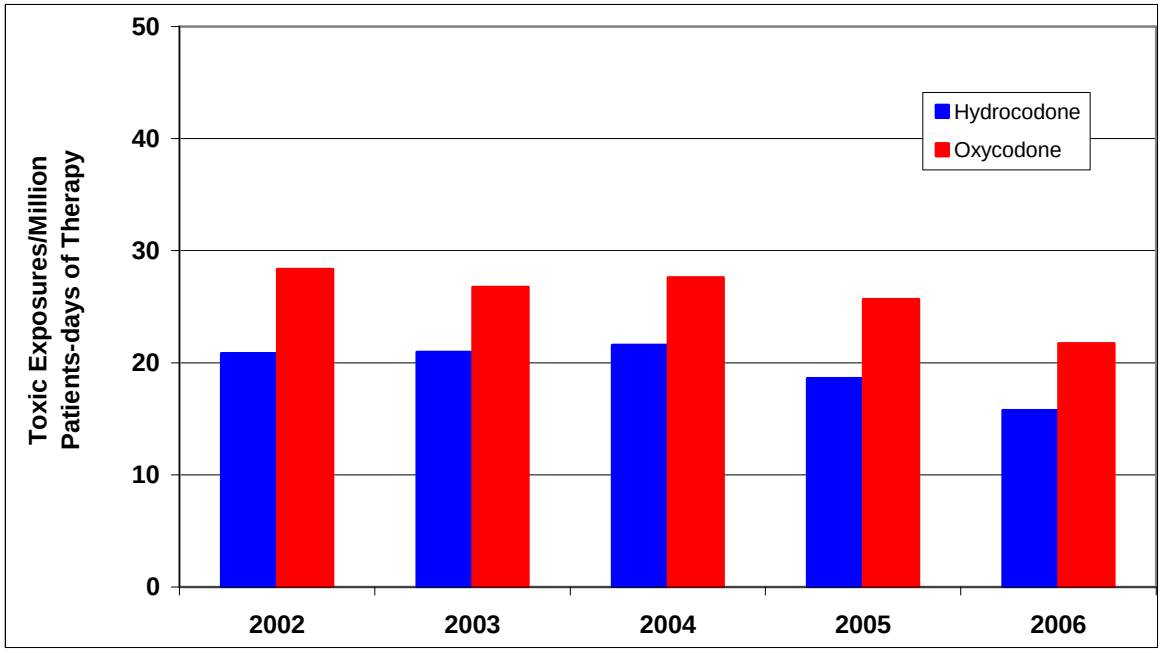
Table 6 and **Figure 2** below show rate estimates calculated using *total number patient-days of therapy* obtained from a different data source by DEPI, which are consistent with the findings above in Table 5 and Figure 1.

Table 6 Hydrocodone and Oxycodone Toxic Exposures per Million Patient-days of Therapy, NPDS 2002-2006*

Year	Hydrocodone			Oxycodone		
	Toxic Exposures	Patients-days of Therapy	Rate of Toxic Exposures per Million Patient-days of therapy	Toxic Exposures	Patients-days of Therapy	Rate of Toxic Exposures per Million Patient-days of therapy
2002	17429	836,376,926	20.84	10515.00	371,403,379	28.31
2003	19578	935,435,900	20.93	11254.00	421,168,069	26.72
2004	22654	1,045,548,234	21.67	12603.00	457,064,703	27.57
2005	22229	1,195,243,650	18.60	13191.00	515,357,743	25.60
2006	22244	1,407,896,816	15.80	13473.00	621,711,530	21.67

**DEPI Analysis. Sources: Total Number Patient-days of Therapy from SDI: Vector One®: National. Extracted 2/11*

Figure 2 Hydrocodone and Oxycodone Toxic Exposures per Million Patient-days of Therapy, NPDS 2002-2006*



**DEPI Analysis. Sources: Total Number Patient-days of Therapy from SDI: Vector One®: National. Extracted 2/11*

DEPI extended DEA's analyses of NPDS data and examined the number of toxic exposures per *Total Number of Extended Units (EU)* (see **Table 7**) and by the *Total Number of Patients* receiving a prescription for hydrocodone and oxycodone (see **Table 8**)

Table 7 Rates of Toxic Exposure for Hydrocodone Combination Products vs. Oxycodone Products, Using Total Number of Extended Units Dispensed as the Denominator, NPDS 2002-2006*

Year	Hydrocodone			Oxycodone		
	Toxic Exposures	Extended Units	Rate of Toxic Exposures per Million Extended Units	Toxic Exposures	Extended Units	Rate of Toxic Exposures per Million Extended Units
2002	17,429	3,876,806,668	4.50	10,515	1,546,235,730	6.80
2003	19,578	4,296,278,651	4.56	11,254	1,774,425,040	6.34
2004	22,654	4,781,976,806	4.74	12,603	1,965,056,695	6.41
2005	22,229	5,403,219,249	4.11	13,191	2,249,811,856	5.86
2006	22,244	6,205,057,454	3.58	13,473	2,717,616,026	4.96

** DEPI Analysis. Source: SDI: Vector One®: National. Extracted 1/11.*

Table 8 Rates of Toxic Exposure for Hydrocodone Combination Products vs. Oxycodone Products, Using Total Number of Patients as the Denominator, National Poison Data System (NPDS) 2002-2006*

Year	Hydrocodone			Oxycodone		
	Total Number of Patients	Toxic Exposures	Rate of Toxic Exposure per 100,000 patients	Total Number of Patients	Toxic Exposures	Rate of Toxic Exposure per 100,000 patients
2002	36,172,841	17,429	48	11,451,324	10,515	92
2003	36,525,332	19,578	54	11,810,749	11,254	95
2004	38,829,275	22,654	58	12,470,568	12,603	101
2005	40,688,681	22,229	55	13,271,375	13,191	99
2006	40,750,793	22,244	55	13,649,693	13,473	99

** DEPI Analysis. Source: SDI: Vector One®: Total Patient Tracker. Extracted 1/11.*

In summary, the analyses using NPDS data demonstrated that when using several patient exposure-based denominators (*Total Number of Prescriptions, Total Patient-days of Therapy, Total Number of Extended Units,* and *Total Number of Patients*) the toxic exposure rate of oxycodone is higher than that for hydrocodone combination products demonstrating a risk profile that is less favorable for oxycodone products. However, similar analyses described in DEA's report (Table 6 and Figure 2) employing population exposure-based denominators (*General Population*) and (*Total Amount of Substance Distributed*) demonstrated that the population exposure based risk due to abuse/misuse of hydrocodone combination products is higher than that associated with the use of oxycodone products.

3.6.2 Drug Abuse Warning Network (DAWN)

3.6.2.1 DEA Analysis of DAWN Data

DEA analysis of DAWN data from 2003 forward is reported separately from data prior to 2003 (1994-2002) due to changes in data reporting methods in 2003.

The rate of Emergency Department (ED) mentions (exposures related to ED visits and death) for oxycodone per 1 million prescriptions was up to 3 times higher than the rate for hydrocodone using the data collected 1998-2002. Similarly, in 2004-2006 the rate of ED mentions per 1 million prescriptions of oxycodone was about 3.5 higher than the corresponding ED mentions for hydrocodone combination products.

When *Total Patient-days of Therapy* was used as the denominator, the rates of ED mentions for hydrocodone combination products were still lower compared to the rates for oxycodone products from 1994-2002 and from 2004-2006.

With the use of *Total Amount of Substance Distributed* as the denominator, the rate of ED mentions for hydrocodone combination products was similar to that corresponding to oxycodone products from 1998-2002 and slightly lower than the rate for oxycodone products from 2004-2006. *[Figure 6 in DEA report demonstrated that there were more ED mentions for oxycodone than for hydrocodone. However, the text on page 26 is inconsistent with this figure.]*

DEA concluded that "DAWN data demonstrate that abuse of hydrocodone combination products similar to oxycodone products has been escalating. The rates of abuse as represented by the number of ED mentions per each kg of hydrocodone distributed in the US is similar (1997-2002) or slightly smaller (2004-2006) that those for oxycodone. The nonnarcotic active ingredients present in hydrocodone combination products do not reduce the abuse potential of hydrocodone."

3.6.2.2 DEPI Comments on DEA Analysis of DAWN Data

DEPI concurs with DEA that the total number of ED mentions for hydrocodone and oxycodone is increasing over time. The absolute number of ED mentions for hydrocodone from 1994-2002 was higher than the corresponding number for oxycodone; however, the absolute number for oxycodone has been higher from 2004 to 2009.

DEPI observed that with the use of *Total Amount of Substance Distributed* as the denominator, the rate of ED mentions for hydrocodone combination products was higher than that corresponding to oxycodone products from 1998-2001 and lower than the rate for oxycodone products in 1997, 2002, and from 2004-2006.

DEPI expanded the analysis of DAWN data by using *Extended Units* (EU) and *Total Number of Patients* as the denominators to estimate rates of toxic exposure and found similar results to those presented when *Total Number of Prescriptions* and *Total Patient-days of Therapy* were used as the denominator. As seen in **Table 9** there were more ED mentions per million EUs for oxycodone products than for hydrocodone combination products. The rate of ED mentions for hydrocodone combination products in 1998 was almost 6 per million EUs increasing to 6.5 ED mentions per million EUs in 2002. For oxycodone, there were more than 7 ED mentions per million EUs in 1998 increasing to 14.5 ED mentions per million EUs in 2002.

Table 9 Number of Emergency Department Mentions per Million Extended Units Dispensed (EU) Reported in DAWN, 1998-2002*

Year	Hydrocodone			Oxycodone		
	ED Mentions	Extended Units	Exposures per Million Extended Units	ED Mentions	Extended Units	Exposures per Million Extended Units
1998	13,611	2,281,027,702	5.97	5,211	724,526,925	7.19
1999	15,252	2,694,717,999	5.66	6,429	911,879,344	7.05
2000	20,098	3,118,342,107	6.45	10,825	1,169,976,923	9.25
2001	21,567	3,490,676,176	6.18	18,409	1,390,549,276	13.24
2002	25,197	3,876,806,668	6.50	22,397	1,546,235,730	14.48

** DEPI Analysis. Sources: Office of Applied Studies, SAMHSA, National Survey on Drug Use and Health; Extended Units from SDI: Vector One®: National. Extracted 1/11.*

DEA asserted that the "nonnarcotic active ingredients present in hydrocodone combination products do not reduce the abuse potential of hydrocodone." Most drug abuse datasets do not differentiate drug abuse events by drug formulation rather only attribute it to the substance. In 2004, however, DAWN did start to collect drug related ED visits by the specific drug product involved.

To assess ED visits related to misuse and abuse the Substance Abuse and Mental Health Services Administration (SAMHSA) developed the case construct: NMUP – the nonmedical use of pharmaceuticals. NMUP combines various types of cases recorded in DAWN. It includes ED visits where the patient exceeded the prescribed or recommended dose, i.e. overmedication, used drugs prescribed for another person, malicious poisoning, or substance abuse (categorized by "other"). **Table 10** summarizes the national estimates of NMUP ED visits associated with hydrocodone combination products as well as for oxycodone products separately for single ingredient and combination products using *Extended Units* dispensed as the denominator.

Table 10 Number of Emergency Department Mentions per Million Extended Units (pills) Dispensed of Hydrocodone Combination Products and Oxycodone Products (single ingredient and combination products) Reported in DAWN, 2004-2009*

Year	Hydrocodone Products			Oxycodone Single Ingredient Products			Oxycodone Combination Products		
	NMUP ED Visits	Extended Units	EDs per Million Extended Units	NMUP ED Visits	Extended Units	EDs per Million Extended Units	NMUP ED Visits	Extended Units	EDs per Million Extended Units
2004	39,844	4,781,976,806	8	26,733	786,896,915	34	17,729	1,178,159,780	15
2005	47,192	5,403,219,249	9	32,301	890,705,061	36	23,959	1,359,106,795	18
2006	57,550	6,205,057,454	9	39,850	1,147,026,099	35	27,916	1,570,589,926	18
2007	65,734	6,931,961,123	9	46,441	1,392,445,161	33	32,775	1,794,942,710	18
2008	89,051	7,446,215,688	12	72,218	1,630,662,600	44	39,209	1,979,771,779	20
2009	86,258	7,760,426,465	11	104,631	1,759,163,446	59	50,868	2,155,539,866	24

** DEPI Analysis. Sources: Office of Applied Studies, SAMHSA, National Survey on Drug Use and Health; Extended Units from SDI: Vector One®: National. Extracted 1/11.*

Table 11 shows the results from the analysis of DAWN data employing total number of patients as a denominator. These results show a higher rate of ED mentions for oxycodone single ingredient and combination products which is consistent with the findings from all previous analyses of DAWN data using patient exposure-based denominators.

Table 11 Rates of Emergency Department Mentions for Hydrocodone Combination Products vs. Oxycodone Single Ingredient and Combination Products, Using Total Number of Patients as the Denominator, DAWN 2004-2009*

Year	Hydrocodone Products			Oxycodone Single Ingredient Products			Oxycodone Combination Products		
	NMUP ED Visits	Total Number of Patients	Rate of EDs Mentions per 100,000 Patients	NMUP ED Visits	Total Number of Patients	Rate of EDs Mentions per 100,000 Patients	NMUP ED Visits	Total Number of Patients	Rate of EDs Mentions per 100,000 Patients
2004	39,844	38,829,275	10	26,733	1,987,475	135	17,729	11,213,265	16
2005	47,192	40,688,681	12	32,301	2,133,796	151	23,959	11,944,413	20
2006	57,550	40,750,793	14	39,850	2,428,152	164	27,916	12,069,999	23
2007	65,734	42,161,912	16	46,441	2,916,381	159	32,775	12,805,097	26
2008	89,051	43,023,767	21	72,218	3,209,855	225	39,209	13,262,589	30
2009	86,258	43,010,258	20	104,631	3,492,401	300	50,868	13,763,269	37

** DEPI Analysis. Sources: Office of Applied Studies, SAMHSA, National Survey on Drug Use and Health; Total Number of Patients from SDI: Vector One®: Total Patient Tracker. Extracted 1/11.*

A similar analysis conducted by DEPI reviewers comparing tramadol single ingredient vs. combination products showed there were 3.4 NMUP ED visits in 2004 for single ingredient

tramadol products and 1.7 NMUP ED visits for tramadol/acetaminophen products. This analysis could not be extended to more years because the amount of drug dispensed for tramadol/acetaminophen products continues to decrease and the national estimates for NMUP ED visits were too low to produce precise estimates.

The results from the above analyses comparing oxycodone and tramadol single ingredient vs. combination products demonstrate that combination products containing opioids generally are associated with lower rates of ED mentions than single ingredient opioid-containing products. These findings could be due to the lower amount of opiate contained in combination products, or to the addition of other products such as acetaminophen, or due to a combination of both factors. These findings likely apply to hydrocodone as well, even though the lack of single-entity hydrocodone products makes it impossible to demonstrate.

In summary, these analyses using DAWN data demonstrated that when using several patient exposure-based denominators, the rate of ED mentions of oxycodone products is higher than that corresponding for hydrocodone combination products demonstrating a risk profile that is less favorable for oxycodone products. In addition, similar analyses employing population-exposure based and patient exposure-based denominators demonstrated that currently the risk due to abuse/misuse of hydrocodone combination products is lower than that associated with the use of oxycodone products, single agent or combined.

3.6.3 Florida Department of Law Enforcement (FDLE) Medical Examiners Data

3.6.3.1 DEA Analysis of the FDLE Medical Examiners Data

DEA presented Florida Department of Law Enforcement (FDLE) data which contains reports from the medical examiners' office on drug related deaths and whether the drug found in the decedent was the "cause" of death or merely present in the body at the time of death.

Between 2005 and 2007 the number of drug-related deaths for hydrocodone and oxycodone increased by 10.4% and 35.8% respectively.

The rates of drug-associated deaths per 1 million patient-days of therapy for oxycodone were higher than the rates for hydrocodone from 2005-2007. The rates were similar for hydrocodone combination products and oxycodone products using total amount of drug sales data as the denominator.

DEA concluded, based on rates of drug-associated deaths, that both hydrocodone and oxycodone on a kilogram basis have similar rates of mortality.

The proportion of drug-related deaths where the drug was determined to be the "cause" of death is consistently higher for oxycodone products than for hydrocodone products (see Table 8 in DEA report). The proportion of deaths where oxycodone was considered to be causal was close to 55% whereas the proportion of deaths where hydrocodone was present and determined by the medical examiner to be the cause of death was approximately 33%. DEA attributes these findings to the differences in formulations (i.e., some oxycodone formulations contain a high amount of drug, which is more likely to cause death when compared to hydrocodone combination products which contain a much smaller amount of drug).

3.6.3.2 DEPI Comments on FDLE Analysis

Although the results derived from the analyses of a database containing only regional information cannot be generalized to the general population in the U.S, the selection of this data source is appropriate to examine the extent of abuse and diversion of hydrocodone combination products in comparison with oxycodone products. Expanded analyses using *Total Number of Extended Units* and *Total Number of Patients* could not be done given DEPI does not have data on the number of extended units and total number of patients for the state of Florida.

Based on FDLE Medical Examiners Data, DEPI concluded that when using a patient exposure-based denominator (*Total Patient-days of Therapy*) the rate of oxycodone-associated deaths was higher than the rate for hydrocodone from 2005-2007 and when using a population exposure based denominator (*Total Amount of Substance Distributed* in kgs) the mortality rate associated with oxycodone was slightly higher in 2005 and 2006 but lower than the corresponding rate for hydrocodone combination products in 2007.

DEA correctly stated that the most likely explanation for the higher number of oxycodone-associated deaths is the differences in pharmaceutical formulations.

3.6.4 National Survey on Drug Use and Health (NSDUH) Data

3.6.4.1 DEA Analysis of NSDUH Data

NSDUH data from 2002-2005 indicate that 57.7% of individuals who first used pain relievers for non-medical indications used hydrocodone and 21.7% used oxycodone. Based on the DHHS review, 7.8% of the total US population age 12 and older are lifetime users of hydrocodone while 4.9% are lifetime users of oxycodone (data from 2005).

The NSDUH data showed that in 2002-2005 the rates of persons who initiated non-medical use for the first time in the past year per 1 million prescriptions for oxycodone was slightly higher (up to 1.5-fold) as compared to the corresponding rates for hydrocodone. When using *Total Patient-days of Therapy* as the denominator, the rates of past year initiates for non-medical for hydrocodone were slightly higher than those of oxycodone products for the same years. However, when using the *Total Amount of Substance Distributed* as the denominator, the rates of past year initiates for non-medical use of hydrocodone combination products were substantially higher than oxycodone products from 2002 to 2005.

The DEA concluded that the nonnarcotic active ingredients present in hydrocodone combination products do not reduce the abuse potential of hydrocodone based on the rates derived from calculations using *Total Amount of Substance Distributed.*

Additional analyses conducted by DEA of NSDUH data included in the DHHS report consisted of a comparison of the incidence of any past year pain reliever use among lifetime users of (1) any pain reliever, (2) hydrocodone combination products, (3) oxycodone products, (4) OxyContin only, (5) oxycodone products other than OxyContin. DEA concluded that the propensity of the lifetime users of OxyContin to have used any pain relievers in the past year was much higher than that of lifetime users of the other products included in the evaluation and that hydrocodone products were a distant second only to OxyContin. DEA concluded that "the dependence potential of hydrocodone combination products is higher than that of oxycodone immediate-release products (schedule II) (i.e., single-entity immediate-release and combination products combined)."

3.6.4.2 DEPI Comments on DEA Analysis of NSDUH Data

The high percentage of individuals who first used hydrocodone (57.7%) and oxycodone (21.7%) for non-medical indications as documented by NSDUH (2002-2005) is a function of hydrocodone's large number of prescriptions and therefore increased availability in comparison to oxycodone and should not be interpreted as a higher abuse potential than oxycodone.
DEPI expanded the analysis of NSDUH data by calculating the rates of past year initiates using *Extended Units* and *Total Number of Patients* as denominators; see **Table 12** and **Table 13.**

Table 12 Rate of Past Year Initiates of Hydrocodone Combination Products and Oxycodone Products per Million Extended Units Dispensed, NSDUH 2002-2005*

Year	Rate of Past Year Initiates per 1 million Extended Units	
	Hydrocodone	**Oxycodone**
2002	0.35	0.31
2003	0.33	0.28
2004	0.28	0.31
2005	0.24	0.20

**DEPI Analysis. Sources: Office of Applied Studies, SAMHSA, National Survey on Drug Use and Health; Extended Units from SDI: Vector One®: National. Extracted 1/11.*

Table 13 Rate of Past Year Initiates of Hydrocodone Combination Products and Oxycodone Products per 1 Million Patients Receiving a Prescription, NSDUH 2002-2005*

Year	Rate of Past Year Initiates per 1 million Patients	
	Hydrocodone	**Oxycodone**
2002	37.3	41.4
2003	38.4	42.6
2004	34.8	48.8
2005	32.3	34.3

**DEPI Analysis. Sources: Office of Applied Studies, SAMHSA, National Survey on Drug Use and Health; Extended Units from SDI: Vector One®: Total Patient Tracker. Extracted 1/11.*

In summary, estimated rates of past year use of hydrocodone combination products employing *Total Patient-days of Therapy* and *Extended Units* as denominators resulted in slightly higher rates for hydrocodone combination products when compared to oxycodone products. However when using *Total Number of Prescriptions* and *Total Number of Patients* as the denominator resulted in the opposite finding; the rates were higher for oxycodone products. These findings suggest that non-medical use of hydrocodone combination products and oxycodone products is similar.

DEPI concurs with DEA's observation that when using *Total Amount of Substance Distributed* in Kgs (population exposure-based denominator) the rates of past year initiates for non-medical use of hydrocodone combination products were higher than the corresponding rates for oxycodone products from 2002 to 2005 suggesting an increased risk of abuse/misuse of hydrocodone products.

3.6.5 Monitoring the Future (MTF) Data

3.6.5.1 DEA Analysis of the Monitoring the Future (MTF) Data

The MTF survey data showed that the annual prevalence of non-medical use of Vicodin (acetaminophen and hydrocodone) was substantially higher than that of OxyContin among high school students. The prevalence ranged from 2.5-3.0% in 8th graders, 6.2-7.2% in 10th graders, and 9.3-10.5% in 12th graders for Vicodin. The corresponding prevalence for OxyContin was 1.3-2.6%, 3.0-3.9%, and 4.0-5.5% for the 8th, 10th, and 12th graders, respectively. DEA concludes that these data support the high abuse potential of hydrocodone combination products.

3.6.5.2 DEPI Comments on DEA Analysis of MTF Data

MTF data must be interpreted in light of the large number of prescriptions dispensed for hydrocodone combination. The higher prevalence of use of hydrocodone combination products (Vicodin) among high school students is likely to be a function of the larger number of prescriptions for hydrocodone combination products and therefore increased availability, and should not be used to make inferences about the risk profile of hydrocodone combination products and oxycodone products.

Nevertheless, DEPI agrees that these data indicate that the substantial abuse of hydrocodone combination products reported in this survey represents a public health problem.

4 DISCUSSION

The objective of the eight-factor analysis is to provide scientific and medical evidence of the abuse and diversion of hydrocodone combination products to support the rescheduling recommendation from Schedule III to Schedule II.

There are significant differences between hydrocodone combination and oxycodone products in composition type (single-entity vs. combination product), total dosage unit per prescription, drug amounts in each dose unit, and in therapeutic use. Thus, it is essential to evaluate the impact of these differences on drug abuse-related health outcomes rates. In addition, study outcomes might be underestimated due to under-reporting. However, the magnitude of potential bias introduced by differences in underreporting between hydrocodone combination products and oxycodone products is unknown.

The use of a different set of denominators to estimate the rates of drug abuse-related health outcomes is at the crux of DEA's analysis of the data included in their response to the DHHS report. The new denominators used in DEA's analyses were *Total Patient-days of Therapy* and *Total Amount of Substance Distributed (sales, in kg)*. The rationale for the use of denominators, rather than *Total Number of Prescriptions,* stems from the fact that the validity of a comparison between rates of drug abuse-related health outcomes depends on how accurately the denominator used in these calculations accounts for drug-to-drug variability in: (1) average days of therapy per prescription, (2) composition type (single-entity vs. combination product), (3) total dosage units per prescription, (4) potency-adjusted drug amounts per each dose unit, and (5) clinical indications. DEA considered that rate estimates calculated utilizing *Total Amount of Substance Distributed* provided the most valid comparison between hydrocodone combination products and its comparator, oxycodone products. Rate estimates generated by DEA using this denominator frequently produced rates of drug abuse-related health outcomes that were similar or higher for hydrocodone which was

interpreted as hydrocodone combination products having an abuse potential comparable to that of oxycodone products.

DEPI's analyses of these data were based on the understanding that inferences made based on drug abuse-related health outcome rates will depend on whether the denominator used is patient exposure-based (characterize patient exposure-based risk profile) or population exposure-based (characterize of population exposure-based risk profile).

When comparing hydrocodone combination products with oxycodone products, the use of *Total Number of Extended Units* dispensed as a denominator generated the best metric of patient exposure-based risk since it accounts for the variability in days of therapy and dosage units per prescription. *Total Number of Patient-days of Therapy* can only account for the variability in days of therapy between hydrocodone combination products and oxycodone products.

Population exposure-based denominators do not account for the variations in drug exposure. The DEA report employs the terms "adjust for", "account for", and "eliminate" to characterize the impact of the use of the different denominators on average days of therapy per prescription, composition type (single-entity vs. combination product), total dosage unit per prescription, potency-adjusted drug amounts per each dose unit, and clinical indications. On page 19 of DEA Report, section 1.2.2.3, third paragraph, DEA states, *"The second reason is that the drug distribution data from ARCOS database, unlike total number of prescriptions and total patient-days of therapy, as a denominator, eliminate variability related to drug-specific differences such as product composition (single-entity versus combination) and formulation (immediate-release versus extended-release), total dosage units per prescription, and drug amounts per dosage unit."* DEPI concurs that this denominator eliminates the variability in the above mentioned factors attributed to the differences between hydrocodone combination products and oxycodone products. However, to make a valid comparison between hydrocodone combination products and oxycodone products, it is important to account for or adjust for these differences.

Rates of drug abuse-related health outcomes calculated using outcomes data from NPDS, DAWN, and FDLE medical examiner and a patient exposure-based denominator were all higher for oxycodone products. However, similarly calculated rates using NSDUH data were slightly lower for oxycodone products when compared to hydrocodone combination products. DEPI concluded that the preponderance of the data suggested that hydrocodone combination products have a more favorable risk profile (abuse potential) than oxycodone products. These findings are consistent with the fact that a substance's abuse potential is a function of dose and potency. Conversely, data from NPDS, DAWN, FDLE medical examiner, NSDUH, and MTF demonstrated a significant population exposure-based risk due to the abuse/misuse of hydrocodone combination products, likely based upon their widespread use and resulting availability.

The risks associated with abuse and misuse of hydrocodone combination products are twofold. One is associated with the opioid ingredient that was captured in the DEA's analyses, including the risks of developing tolerance, dependence, addiction, and mortality. The second is associated with the non-narcotic active ingredient, such as acetaminophen that is contained in about 90% of all hydrocodone combination products. A severe and potentially fatal adverse event associated with acetaminophen overdose is hepatic necrosis. However, a detailed discussion on the adverse effects of acetaminophen overdose is outside the scope of this review.

A major limitation of these analyses is the inability to calculate confidence intervals around estimates, which eliminates our ability to make statistical comparisons between hydrocodone

products and oxycodone products. Given the relatively small numerator counts and large denominators, it is possible that confidence intervals, if calculable, would be large and may overlap – prohibiting discrimination between outcome rates for these two products. However, this cannot be known for certain and we are left with only the ability to informally compare rates, which we have done to the best of our ability in this review.

5 CONCLUSIONS

- The assessment of the abuse and misuse of hydrocodone combination products must include both analyses of the population exposure-based risk profile and the patient exposure-based risk profile.
- The selection of oxycodone products as a comparator to hydrocodone combination products is reasonable.
- Population exposure-based and patient exposure-based drug abuse-related health outcome rates are important metrics to consider in the evaluation of the public health impact and risk profile of hydrocodone combination products.
- Population -exposure based rates provide a way to assess a product's abuse/misuse risk profile from a community perspective while patient exposure-based rates provide a metric to assess the abuse/misuse risk from a patient's perspective.
- Of the patient exposure-based denominators assessed in this review, drug abuse-related health outcomes rate estimates using *Extended Units* dispensed as a denominator likely provided the best metric of patient exposure-based risk, while *Total Amount of Substance Distributed* likely provided the best metric of population exposure-based risk.
- The preponderance of the data evaluated in this review indicated that, in spite of the significantly larger volume of prescriptions of hydrocodone combination products, these products have a lower risk profile than oxycodone products. However, these data also demonstrated the abuse/misuse of hydrocodone combination products represents a significant risk to the community.
- The data analyzed in this review do not support DEA's theory that nonnarcotic active ingredients (acetaminophen, ibuprofen, aspirin, chlorpheniramine, or homatropine) present in hydrocodone combination products do not reduce the abuse potential of hydrocodone.

APPENDIX

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.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

Appendix Table 1: Total Number of Dispensed Prescriptions for Hydrocodone Combination Products and Oxycodone Products by Form through U.S. Outpatient Retail Pharmacies, 1998-2009

Year	Hydrocodone	Oxycodone Products				
	Hydrocodone Combination Products	Total Market	IR Combination Products	Single-ingredient Total	Single-ingredient ER	Single-ingredient IR
1998	62,085,209	15,873,926	13,717,598	2,156,328	1,713,093	443,235
1999	70,663,749	18,711,308	14,730,731	3,980,577	3,225,822	754,755
2000	78,194,168	22,510,714	15,849,492	6,661,222	5,462,496	1,198,726
2001	83,831,501	25,445,684	17,230,958	8,214,726	6,558,762	1,655,964
2002	88,986,486	26,671,722	18,479,453	8,192,269	6,225,475	1,966,794
2003	93,465,569	29,219,075	20,219,335	8,999,740	6,595,324	2,404,416
2004	99,015,543	31,269,308	22,050,084	9,219,224	6,303,494	2,915,730
2005	106,661,154	34,497,195	24,454,184	10,043,011	6,427,090	3,615,921
2006	113,727,247	38,524,757	26,303,610	12,221,148	7,423,270	4,797,878
2007	120,558,365	43,405,134	28,803,782	14,601,351	8,296,909	6,304,427
2008	124,638,176	47,225,509	30,805,889	16,419,621	8,325,977	8,093,536
2009	123,785,711	49,419,388	32,239,395	17,179,993	8,045,237	9,134,756

Source: SDI: Vector One®: National. Extracted 1/11

Appendix Table 2: Total Number of Days of Therapy for Hydrocodone Combination Products and Oxycodone Products by Form through U.S. Outpatient Retail Pharmacies, 1998-2009

Year	Hydrocodone	Oxycodone Products				
	Hydrocodone Combination Products	Total Market	IR Combination Products	Single-ingredient Total	Single-ingredient ER	Single-ingredient IR
1998	486,252,907	158,198,745	111,288,212	46,910,533	40,667,828	6,242,705
1999	577,429,768	210,834,472	122,206,120	88,628,352	77,574,763	11,053,589
2000	670,487,966	285,719,450	135,361,283	150,358,167	132,319,778	18,038,389
2001	756,776,243	344,253,803	153,487,288	190,766,515	164,584,174	26,182,341
2002	836,376,926	371,403,379	176,255,955	195,147,424	162,474,795	32,672,629
2003	935,435,900	421,168,069	205,739,929	215,428,140	174,149,054	41,279,086
2004	1,045,548,234	457,064,703	236,427,568	220,637,135	168,391,946	52,245,189
2005	1,195,243,650	515,357,743	275,262,589	240,095,154	173,071,276	67,023,878
2006	1,407,896,816	621,711,530	325,577,930	296,133,600	201,701,293	94,432,307
2007	1,590,153,590	729,530,018	372,818,370	356,711,648	227,493,854	129,217,328
2008	1,714,383,720	816,911,754	416,875,085	400,036,669	228,347,257	171,686,295
2009	1,785,201,029	886,181,110	461,214,050	424,967,060	221,323,665	203,643,395

Source: SDI: Vector One®: National. Extracted 2/11.

Appendix Table 3: The Average Number of Days of Therapy Dispensed to Patients for Hydrocodone Combination Products and Oxycodone Products by Form through U.S. Outpatient Retail Pharmacies, 1998-2009

Year	Hydrocodone	Oxycodone Products			
	Hydrocodone Combination Products	Total Market	IR Combination Products	Single-ingredient ER	Single-ingredient IR
1998	7.8	10.0	8.1	23.7	14.1
1999	8.2	11.3	8.3	24.0	14.6
2000	8.6	12.7	8.5	24.2	15.0
2001	9.0	13.5	8.9	25.1	15.8
2002	9.4	13.9	9.5	26.1	16.6
2003	10.0	14.4	10.2	26.4	17.2
2004	10.6	14.6	10.7	26.7	17.9
2005	11.2	14.9	11.3	26.9	18.5
2006	12.4	16.1	12.4	27.2	19.7
2007	13.2	16.8	12.9	27.4	20.5
2008	13.8	17.3	13.5	27.4	21.2
2009	14.4	17.9	14.3	27.5	22.3

Source: SDI: Vector One®: National. Extracted 1/11.

Appendix Table 4: Total Number of Extended Units (Pills) Dispensed for Hydrocodone Combination Products and Oxycodone Products by Form through U.S. Outpatient Retail Pharmacies, 1998-2009

Year	Hydrocodone	Oxycodone Products		
	Hydrocodone Combination Products	Total Market	IR Combination Products	Single-ingredient Total
1998	2,281,027,702	724,526,925	568,050,176	156,476,749
1999	2,694,717,999	911,879,344	625,975,512	285,903,832
2000	3,118,342,107	1,169,976,923	695,980,999	473,995,924
2001	3,490,676,176	1,390,549,276	778,609,432	611,939,844
2002	3,876,806,668	1,546,235,730	884,737,163	661,498,567
2003	4,296,278,651	1,774,425,040	1,027,850,734	746,574,306
2004	4,781,976,806	1,965,056,695	1,178,159,780	786,896,915
2005	5,403,219,249	2,249,811,856	1,359,106,795	890,705,061
2006	6,205,057,454	2,717,616,026	1,570,589,926	1,147,026,099
2007	6,931,961,123	3,187,387,872	1,794,942,710	1,392,445,161
2008	7,446,215,688	3,610,434,379	1,979,771,779	1,630,662,600
2009	7,760,426,465	3,914,703,312	2,155,539,866	1,759,163,446

Source: SDI: Vector One®: National. Extracted 1/11.

Appendix Table 5: Total Number of Patients Receiving a Prescription for Hydrocodone Combination Products and Oxycodone Products by Form through U.S. Outpatient Retail Pharmacies, 2002-2009

Year	Hydrocodone	Oxycodone Products				
	Hydrocodone Combination Products	Total Market	IR Combination Products	Single-ingredient Total	Single-ingredient ER	Single-ingredient IR
2002	36,172,841	11,451,324	10,146,929	1,935,059	1,533,431	684,352
2003	36,525,332	11,810,749	10,494,126	2,002,989	1,498,726	800,809
2004	38,829,275	12,470,568	11,213,265	1,987,475	1,344,185	925,401
2005	40,688,681	13,271,375	11,944,413	2,133,796	1,313,419	1,118,429
2006	40,750,793	13,649,693	12,069,999	2,428,152	1,403,903	1,382,379
2007	42,161,912	14,809,175	12,805,097	2,916,381	1,580,498	1,771,363
2008	43,023,767	15,513,521	13,262,589	3,209,855	1,558,002	2,146,120
2009	43,010,258	16,129,421	13,763,269	3,492,401	1,555,399	2,432,554

Source: SDI: Vector One®: Total Patient Tracker. Extracted 1/11.

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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
Office of Pharmacovigilance and Epidemiology

Addendum to July 30, 2009 Epidemiological Analysis of Hydrocodone-containing Products used as Antitussives

Date:	September 14, 2012
To:	Corinne P. Moody Science Policy Analyst Controlled Substances Staff
Through:	Judy Staffa, Ph.D., R.Ph. Director Division of Epidemiology II
From:	Catherine Dormitzer, PhD, MPH Epidemiologist Division of Epidemiology Office of Surveillance of Epidemiology Hina Mehta, PharmD Drug Use Data Analyst Division of Epidemiology Office of Surveillance and Epidemiology
Subject:	Update of the Epidemiological Analysis of Hydrocodone containing products
Drug Name(s):	Hydrocodone-containing products used as antitussives
OSE RCM #:	2012-1613
Application Type/Number	22-279, 22-441, 22-440, 22-439

1 INTRODUCTION

In preparation for the Drug Safety and Risk Management Advisory Committee being held October 29-30, 2012 this memo reviews data from the Drug Abuse Warning Network (DAWN) and IMS Health, Vector One®: National (VONA) for years 2008 and 2009, so that the data provided on assessing risk for abuse related to hydrocodone-containing products used as antitussives are for the same time period as the data provided on assessing risk for abuse related to hydrocodone-containing products used for analgesia (see review dated 2/9/2011).

This memo is an update to a July 30, 2009 review prepared for the Controlled Substance Staff (CSS). That review was an evaluation of the abuse of hydrocodone-containing products used as antitussives. The Office of Surveillance and Epidemiology (OSE), Division of Epidemiology II (DEPI-II) provides data from DAWN as well as drug utilization data for hydrocodone-containing products grouped as antitussive products (cough/cold) for years 2008 and 2009 to update the data presented in the original July 30, 2009 review that covered years 2004-2007. For an update on the data examining the abuse of hydrocodone-containing products for analgesia, see review dated February 9, 2011.

2 METHODS AND MATERIALS

2.1 EPIDEMIOLOGIC ANALYSIS

This analysis uses data on the number of prescriptions dispensed for hydrocodone-containing products using IMS Health, Vector One®: National (VONA) and DAWN, a hospital-based surveillance system run by the Substance Abuse and Mental Health Services Administration (SAMHSA) that examines drug related emergency room visits (see Appendix for database descriptions).

National estimates were provided for emergency department (ED) visits associated with hydrocodone-containing products classified as antitussive products. ED visits associated with hydrocodone-containing products were examined for all misuse/abuse (AllMA). AllMA cases are a SAMHSA-defined construct that combines various types of cases of ED visits recorded in DAWN. "AllMA" includes all of the following case types:

- Overmedication
- Malicious poisoning
- Other (by design, most cases of documented drug abuse will fall into this category), and
- Any ED visit where the use of an illicit drug or alcohol is noted in the ED visit record and is involved in the event.

An "abuse ratio" was calculated by dividing the number of AllMA ED visits by 10,000 prescriptions dispensed.

3 RESULTS

3.1 OUTPATIENT DISPENSED PRESCRIPTIONS -- VONA

Table A.1 in the Appendix shows the total number of prescriptions dispensed in the outpatient retail setting (mail order excluded) for all hydrocodone-containing products. During year 2009, approximately 130 million prescriptions for hydrocodone-containing products were dispensed of which, approximately 124 million prescriptions (95% of total) were dispensed for analgesic hydrocodone-containing combinations and 6 million (5% of total) prescriptions for hydrocodone antitussive products. Overall, as shown in Table 3.1, the number of prescriptions dispensed for hydrocodone antitussive products decreased by 35% from year 2004 to 2009.

3.2 NATIONAL ESTIMATES OF ALLMA EMERGENCY DEPARTMENT (ED) ED VISITS (DAWN)

Table 3.1 shows the national estimates of "AllMA" (i.e. all misuse/abuse) ED visits associated with antitussive hydrocodone-containing products, as well as "abuse ratios" for each category. In contrast to the national estimates generated for 2004-2007, national estimates and confidence intervals could not be generated for 2008 and 2009. The relative standard error (RSE[1]) for the national estimates for hydrocodone-containing antitussive combination products for these years were too large to produce estimates that could be regarded as precise. Therefore, estimates were suppressed for these years and abuse ratios could not be calculated.

Table 3.1: Summary of National Estimates of all abuse/misuse (AllMA) ED Visits Reported in DAWN and Number of ED Visits per 10,000 Prescriptions for Antitussive Hydrocodone-Containing Products -- 2004 -2009

AllMA ED Visits	*2004*	*2005*	*2006*	*2007*	*2008*	*2009*
Antitussive Hydrocodone	389	333	929	616	…	…
95% CI	...	...	...	(116, 1,115)	…	…
Hydrocodone prescriptions						
Antitussive Hydrocodone	9,416,226	11,884,023	10,811,732	10,299,374	8,684,459	6,139,354
Abuse Ratios*						
Antitussive Hydrocodone	0.4	0.3	0.9	0.6	…	…

*abuse ratio = number of ED visits/10,000 prescriptions
… = estimates/confidence intervals were not provided if associated relative standard error (RSE) is greater than 50
Sources: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, IMS Health, Vector One®: National. Data Extracted 9-12-12.

4 DISCUSSION

As can be seen in Table 1, the addition of the years 2008 and 2009 could not produce valid AllMA national estimates for antitussive hydrocodone-containing products because reliable

[1] Relative standard error (RSE) 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.

estimates could not be produced. As a result, the evaluation of antitussive hydrocodone-containing products do not substantially contribute to the examination of the abuse profile of hydrocodone-containing products.

The inability to produce reliable estimates most likely is due to a low number of events, i.e. AllMA related ED visits associated with hydrocodone-containing antitussive products. It is also possible that this decrease is the result of decreased utilization of antitussive hydrocodone-containing products which represent only 5% of the total amount of hydrocodone-containing prescriptions dispensed in 2009. During year 2007, antitussive hydrocodone-containing products accounted for approximately 8% (10,299,374 prescriptions) of all hydrocodone prescriptions (analgesic and antitussive) dispensed, however in 2009, these products accounted for only 5% (6,139,354 prescriptions) of all hydrocodone prescriptions dispensed, accounting for a 40% decrease in dispensed prescriptions of antitussive hydrocodone-containing products.

It is important to note the following limitations of this analysis. The estimates provided are not true ratios or rates. Each dataset (DAWN and IMS) has different sampling methodologies, different populations and different methods for calculating point estimates and respective confidence intervals. Furthermore, these data are not linked; for each dataset, data are collected independently. The individuals who went to the emergency room may also not have had a legitimate prescription for the drug associated with the ED visit.

Another important limitation is that DAWN data represents patients that were able to make it to the emergency room. Any deaths that occur prior to an ED visit will not be captured using DAWN ED data. Conversely, it is also possible that abuse of these antitussive products does not result in a severe enough event to warrant an ED visit. Lastly, this analysis provides one estimate that includes a variety of antitussive hydrocodone-containing product combinations and as a result, inferences of these products in particular cannot be made.

5 CONCLUSION

Addition of the years 2008 and 2009 could not produce valid AllMA national estimates of abuse for antitussive hydrocodone-containing products because reliable estimates could not be produced. The inability to produce reliable estimates is most likely due to a low number of events, i.e. AllMA related ED visits associated with hydrocodone-containing antitussive products. It is also possible that this decrease is the result of decreased utilization of antitussive hydrocodone-containing products which represent only 5% of the total amount of hydrocodone-containing prescriptions dispensed in 2009. As a result, the evaluation of antitussive hydrocodone-containing products does not substantially contribute to the examination of the overall abuse profile of hydrocodone-containing products

APPENDIX

IMS, Vector One®: National (VONA)

The IMS, Vector One®: National (VONA) database 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 sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

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 (ED) 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.

Table A.1: Total Dispensed Prescriptions for Hydrocodone-containing Products

Total Dispensed Prescriptions for Hydrocodone Products through U.S. Outpatient Retail Pharmacies, 2008-2009

	2008		2009	
	TRxs N	*Share %*	TRxs N	*Share %*
TOTAL MARKET	**133,322,635**	***100.0%***	**129,925,065**	***100.0%***
Hydrocodone Analgesic Products	124,638,176	*93.5%*	123,785,711	*95.3%*
Hydrocodone Antitussive Products	8,684,459	*6.5%*	6,139,354	*4.7%*

Source: IMS Health, Vector One®: National. Data Extracted 9-12-12.
File: VONA 2009-2039 Hydrocodone Products Analgesics and Cough Cold 9-12-12.xls

Table A.2: List of Analgesic and Antitussive Hydrocodone-containing Products

Drug ID	*Drugs of interest*	Category
d03075	hydrocodone	Analgesic
d03428	acetaminophen-hydrocodone	Analgesic
d03429	aspirin-hydrocodone	Analgesic
d04225	hydrocodone-ibuprofen	Analgesic
d03352	hydrocodone-pseudoephedrine	Antitussive
d03353	hydrocodone-phenylpropanolamine	Antitussive
d03366	hydrocodone/phenylephrine/pyrilamine	Antitussive
d03375	hydrocodone/pheniramine/PE/PPA/pyrilamine	Antitussive
d03915	hydrocodone-potassium guaiacolsulfonate	Antitussive
d04152	hydrocodone-phenylephrine	Antitussive
d04350	hydrocodone/potassium guaiacolsulfonate/PSE	Antitussive
d06669	hydrocodone/pseudoephedrine/triprolidine	Antitussive
d05426	brompheniramine/hydrocodone/phenylephrine	Antitussive
d04880	brompheniramine/hydrocodone/pseudoephedrine	Antitussive
d07067	chlorpheniramine/guaifenesin/hydrocodone/PSE	Antitussive
d03361	chlorpheniramine/hydrocodone/phenylephrine	Antitussive
d03416	chlorpheniramine/hydrocodone/PSE	Antitussive
d03356	chlorpheniramine-hydrocodone	Antitussive
d06058	dexbrompheniramine/hydrocodone/phenylephrine	Antitussive
d05365	dexchlorpheniramine/hydrocodone/phenylephrine	Antitussive
d04925	diphenhydramine/hydrocodone/phenylephrine	Antitussive
d03420	guaifenesin/hydrocodon/pheniram/PPA/pyrilamin	Antitussive
d03414	guaifenesin/hydrocodone/pheniramine/PE/PPA	Antitussive
d03403	guaifenesin/hydrocodone/phenylephrine	Antitussive
d03404	guaifenesin/hydrocodone/pseudoephedrine	Antitussive
d03396	guaifenesin-hydrocodone	Antitussive

Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

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

Drug Utilization Review

Date:	September 24, 2012
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Subject:	Drug Utilization for Hydrocodone-Containing Combination Products and Comparators
Drug Name(s):	Combination Hydrocodone-Containing Products and Comparators: oxycodone, morphine, hydromorphone
Application Type/Number:	Multiple
Applicant/sponsor:	Multiple
OSE RCM #:	2012-1613

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EXECUTIVE SUMMARY

In preparation for the Drug Safety and Risk Management Advisory Committee scheduled on October 29 and 30, 2012, this review examines drug utilization patterns for combination hydrocodone-containing products as compared to selected other opioid analgesics from year 2007 through 2011. Because the majority of hydrocodone-containing combination products were sold to U.S. outpatient retail pharmacies, this review focused on the outpatient retail pharmacy drug utilization patterns.

Summary of Findings:

- In year 2011, approximately 96% (131 million prescriptions) of combination hydrocodone-containing prescriptions dispensed through U.S. outpatient retail pharmacies were for the analgesic products and approximately 4% (5.3 million prescriptions) were for antitussive products.
- During year 2011, approximately 47.1 million patients received dispensed prescriptions for combination hydrocodone-containing prescriptions followed by 15.1 million patients receiving dispensed prescriptions for combination oxycodone-containing prescriptions.
- The greatest proportion of combination hydrocodone-containing prescriptions dispensed was prescribed by General Practice/Family Medicine/Osteopathic specialists followed by Internal Medicine.
- The average days of therapy for both combination hydrocodone-containing and combination oxycodone-containing prescriptions was approximately 14 days per prescription as compared to 27 days for single-ingredient extended-release oxycodone and 28 days for extended-release morphine prescriptions.
- According to a crude duration of use analysis, 50% of patients with combination hydrocodone-containing and combination oxycodone-containing prescription claims had therapy duration of 8 days and 6 days, respectively.
- According to U.S. office-based physician practices, the most common diagnoses codes associated with combination hydrocodone-containing products were for "Diseases of the Musculoskeletal System and Connective Tissue" (ICD-9 codes 710-739) followed by "Diseases of Respiratory System" (ICD-9 codes 462-493), and "Fractures, Sprains, Contusions and Injuries" (ICD-9 codes 800-999).

1 INTRODUCTION

The Controlled Substances Staff (CSS) is reviewing a request from the Drug Enforcement Agency (DEA) to reschedule hydrocodone combination products from Schedule III to Schedule II. In support of this assessment, the Division of Epidemiology was requested to provide the outpatient retail drug utilization patterns for combination hydrocodone-containing products and selected comparator drug products: combination oxycodone-containing products, single-ingredient immediate-release oxycodone, single-ingredient extended-release oxycodone, immediate-release morphine, extended-release morphine, and hydromorphone from year 2007 through year 2011, annually.

2 BACKGROUND

2.1 PRODUCT LABELLING

Hydrocodone is an opioid agonist indicated for symptomatic relief of moderate to moderately severe pain in combination with acetaminophen or NSAIDS; as well as, symptomatic relief of

nonproductive cough in combination with antitussives or expectorants.[1,2] Under the Controlled Substance Act (CSA), the Drug Enforcement Administration (DEA), classifies single ingredient hydrocodone as Schedule II controlled substance (not currently marketed) and combination hydrocodone products containing less than 15mg of hydrocodone per dosage unit (such as hydrocodone/acetaminophen, hydrocodone/chlorpheniramine) as Schedule III controlled substances.[3] The Controlled Substances Staff (CSS) received a request from the DEA for a scientific and medical evaluation and scheduling recommendation to re-classify hydrocodone-containing products to Schedule II controlled substances. On October 29 and 30, 2012 the Drug Safety and Risk Management Advisory Committee will be convened to discuss the public health benefits and risks of reclassifying hydrocodone-containing products to Schedule II controlled substances.

2.2 PRODUCTS INCLUDED[4]

Hydrocodone-containing combination products (analgesics) utilization is compared to the following various single ingredient and combination opioid analgesics.
Of note, all the comparator drugs are Schedule II controlled substances.

Drug	
Combination hydrocodone-containing products	Hydrocodone/Acetaminophen Hydrocodone/Ibuprofen Hydrocodone/Aspirin
Combination oxycodone-containing products	Oxycodone/Acetaminophen Oxycodone/Ibuprofen Oxycodone/Aspirin
Single-ingredient oxycodone products	Immediate-release oxycodone Extended-release oxycodone
Morphine sulfate	Immediate-release morphine sulfate Extended-release morphine sulfate
Hydromorphone	Immediate-release hydromorphone Extended-release hydromorphone

3 METHODS AND MATERIALS

3.1 DETERMINING SETTING OF CARE

The IMS Health, IMS National Sales Perspectives™ database (see ***Appendix 2*** for full database description) was used to determine the various retail and non-retail channels of distribution for

[1] http://www.drugs.com/monograph/hydrocodone-bitartrate.html
[2] http://www.deadiversion.usdoj.gov/drugs_concern/hydrocodone.pdf
[3] http://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf
[4] http://www.accessdata fda.gov/scripts/cder/drugsatfda/index.cfm

hydrocodone. Sales data for year 2011 indicated that approximately 95% of hydrocodone-containing products were sold as combination hydrocodone/acetaminophen of which, approximately 65% of combination hydrocodone/acetaminophen bottles (Eaches) were distributed to outpatient retail pharmacies, 28% to non-retail settings; and 7% to mail order pharmacies. Retail pharmacies include chain stores, independent pharmacies, and food store pharmacies.[5] As a result, outpatient retail pharmacy utilization patterns were examined. Neither mail-order/specialty pharmacies nor non-retail settings data were included in this analysis.

3.2 DATA SOURCES USED

Proprietary drug use databases were used to conduct this analysis. (See ***Appendix 2***).

The IMS Health, IMS National Sales Perspective™ database was used to obtain the estimated weight in kilograms of selected opioids, which include combination hydrocodone-containing products, combination oxycodone-containing products, single-ingredient immediate-release oxycodone, single-ingredient extended-release oxycodone, immediate-release morphine, extended-release morphine, and hydromorphone sold from manufacturers to various channels of distribution for years 2007 through 2011. Additionally, the sales distribution of combination hydrocodone-containing antitussive products was examined in terms of extended units (number of tablets, capsules, milliliters, etc.). These sales data represent the amount of product being sold from manufacturers into the "back door" of various drug distribution outlets such as retail pharmacies, hospitals, clinics, etc.; it does not reflect what is being sold to or administered to patients directly.

U.S. outpatient retail pharmacy drug utilization for combination hydrocodone/acetaminophen, combination oxycodone-containing products, single-ingredient immediate-release oxycodone, single-ingredient extended-release oxycodone, immediate-release morphine, extended-release morphine, and hydromorphone was obtained from the IMS Health, Vector One®: National (VONA) and Total Patient Tracker (TPT) databases. From these two sources, nationally projected estimates of the number of prescriptions dispensed and unique patients who received a dispensed prescription were obtained for years 2007 through year 2011, annually. Additionally, the average days of therapy dispensed to patients for a product (therapy days divided by prescriptions) and top specialties prescribing selected opioids were also obtaining from IMS Health, Vector One®: National (VONA).

Diagnoses associated with the use of combination hydrocodone/acetaminophen and comparator drugs were obtained from the Encuity Research, LLC., Physician Drug and Diagnosis Audit™ (PDDA) for years 2007-2011, cumulative.

3.3 DURATION OF THERAPY METHODOLOGY

The Source Healthcare Analytics' ProMetis Lx® Concurrent Product Analyzer (CPA) was used to examine the therapy duration episode for combination hydrocodone-containing products, combination oxycodone-containing products, single-ingredient immediate-release oxycodone, and single-ingredient extended-release oxycodone in deciles to determine the length of therapy for patients using these products for year 2010 through 2011, cumulative. An episode is defined as the period of time that a patient has uninterrupted therapy with a product or group of products

[5] IMS Health, National Sales Perspectives™. Extracted Sept 2012. File: NSPC 2012-1613 Hydrocodone combo sales 09-17-12.xlsx

(regimen). The duration of an episode is the number of days between the start and end dates of the episode, which is determined by summing days' supply of all prescriptions. The total episode duration is the sum of the days for each episode for a product within the selected study period. Product deciles are based on a frequency distribution of the therapy durations for each patient having the specified product. Based on the minimum and the maximum therapy duration, patients are divided into 10 equal groups or deciles.

4 RESULTS

4.1 SALES DISTRIBUTION OF COMBINATION HYDROCODONE-CONTAINING PRODUCTS (ANALGESICS) AND COMPARATOR DRUGS

Figure 1 in Appendix 1 shows the weight in kilograms of combination hydrocodone-containing products, combination oxycodone-containing products, single-ingredient extended-release oxycodone, single-ingredient immediate-release oxycodone, extended-release morphine, immediate-release morphine, and hydromorphone; sold from manufacturers to various channels of distribution for years 2007 through 2011. Throughout the time examined, the weight in kilograms sold of combination hydrocodone-containing products has been the market lead when compared to the selected opioids analyzed. Approximately 64,000 kilograms of combination hydrocodone-containing products were sold during year 2011 accounting for a 28% increase from 50,000 kilograms sold during year 2007. There was more than a 3-fold increase in the weight in kilograms sold of immediate-release oxycodone from 10,000 kilograms sold during year 2007 to about 33,000 kilograms sold during year 2011. The weight in kilograms sold of extended-release oxycodone stayed relatively steady until year 2010 after which there was a 25% decrease to about 19,000 kilograms sold. The other agents analyzed such as combination oxycodone-containing products, extended-release morphine, immediate-release morphine, and hydromorphone have gradually increased in the amount of kilograms sold during the time period examined.

4.2 SALES DISTRIBUTION OF HYDROCODONE-CONTAINING ANTITUSSIVES

Figure 2 in Appendix 1 shows the number of extended units (tablets/capsules/mls) of combination antitussive hydrocodone-containing products sold from the manufactures to various channels of distribution from year 2007 through 2011. The number of extended units sold for combination antitussive hydrocodone-containing products decreased by 59% from approximately 1.9 billion extended units sold during year 2007 to approximately 772 million extended units sold during year 2011.

4.3 OUTPATIENT DISPENSED PRESCRIPTIONS FOR HYDROCODONE COMBINATION PRODUCTS (ANALGESICS AND ANTITUSSIVES)

Table 1 in Appendix 1 shows the estimated number of prescriptions for combination hydrocodone-containing products, stratified as analgesics and antitussives, dispensed from U.S. outpatient pharmacies for years 2007 through 2011. Throughout the time period examined, analgesic combination hydrocodone-containing products accounted for the majority of prescriptions (91%-96% of total) dispensed.

During year 2011 approximately 131 million analgesic combination hydrocodone-containing prescriptions were dispensed through U.S. outpatient retail pharmacies. The number of antitussive combination hydrocodone-containing prescriptions dispensed decreased from

approximately 12 million prescriptions (9% of total) during year 2007 to approximately 5.3 million prescriptions (4% of total) during year 2011.

4.4 Outpatient Dispensed Prescriptions for combination Hydrocodone-containing Products (analgesics) and comparators

Table 2 in Appendix 1 shows the estimated number of combination hydrocodone-containing products, combination oxycodone-containing products, single-ingredient immediate-release oxycodone, single-ingredient extended-release oxycodone, immediate-release morphine, extended-release morphine, and hydromorphone dispensed from U.S. outpatient retail pharmacies for years 2007 through 2011. Throughout the time period examined, combination hydrocodone-containing products accounted for the majority of prescriptions (66%-70% of total) dispensed followed by oxycodone-containing products (25%-29% of total). During year 2011, approximately 131 million (66% of total) combination hydrocodone-containing prescriptions were dispensed followed by 57 million (29% of total) oxycodone-containing prescriptions of which, 34.6 million were of combination oxycodone-containing products and 22.3 million were of single-ingredient oxycodone. Of the single-ingredient oxycodone prescriptions dispensed approximately 16.6 million (74% of single-ingredient oxycodone) prescriptions dispensed were immediate-release oxycodone and about 5.7 million (26% of single-ingredient oxycodone) were extended-release oxycodone during year 2011. Approximately 7.6 million (4% of total) morphine prescriptions were dispensed and 2.7 million (1% of total) hydromorphone prescriptions were dispensed during year 2011. The number of prescriptions dispensed increased for all of the agents analyzed with the exception of extended-release oxycodone which decreased during the time examined.

4.5 Number of Patients Receiving Hydrocodone-Containing Products (analgesics) and Comparators Drugs

Figure 3 in Appendix 1 shows the estimated number of unique patients receiving combination hydrocodone-containing products, combination oxycodone-containing products, single-ingredient immediate-release oxycodone, single-ingredient extended-release oxycodone, immediate-release morphine, extended-release morphine, and hydromorphone dispensed from outpatient retail pharmacies for years 2007 through 2011. Throughout the time period examined, a greater number of patients received combination hydrocodone-containing prescriptions followed by patients receiving combination oxycodone-containing prescriptions. During year 2011, approximately 47.1 million patients received dispensed prescriptions for combination hydrocodone-containing prescriptions followed by 15.1 million patients receiving dispensed prescriptions for combination oxycodone-containing prescriptions. Approximately 4.1 million patients received dispensed immediate-release oxycodone prescriptions while 1.2 million patients received dispensed extended-release oxycodone prescriptions during year 2011. The number of patients receiving dispensed prescriptions increased for all of the agents analyzed with the exception of extended-release oxycodone in which the number of patients decreased during the time examined.

4.6 Top Prescribers

Table 3 in Appendix 2 provides the number of outpatient retail dispensed prescriptions for combination hydrocodone-containing products, combination oxycodone-containing products, single-ingredient immediate-release oxycodone single-ingredient extended-release oxycodone, immediate-release morphine, extended-release morphine, and hydromorphone by top prescribing

specialties. Over the cumulative time period from year 2007 to year 2011, General Practice/Family Medicine/Doctor of Osteopathy specialists were the top prescribing specialty accounting for approximately one-fifth to one-quarter of total prescriptions dispensed for each agent analyzed. Internal Medicine specialists followed accounting for approximately 13%-18% of total prescriptions dispensed for each agent analyzed. Dentists accounted for approximately 10% (65 million prescriptions) of the total combination hydrocodone-containing prescriptions dispensed and approximately 5% (8.6 million prescriptions) of the total combination oxycodone-containing prescriptions dispensed. The number of dispensed prescriptions prescribed by orthopedic surgeons was relatively higher for combination hydrocodone-containing products (8% or 52 million prescriptions) and combination oxycodone-containing products (9% or 14.2 million prescriptions) as compared to the other opioid analgesics analyzed: extended-release oxycodone (4% or 1.5 million prescriptions), immediate-release oxycodone (4% or 2.4 million prescriptions), extended-release morphine (1% or 313,000 prescriptions), immediate-release morphine (less than 1% or 49,000 prescriptions), and hydromorphone (5% or 547,000 prescriptions). In contrast, the number of prescriptions prescribed by anesthesiologists was relatively lower for combination hydrocodone-containing products (3% or 16.3 million prescriptions) and combination oxycodone-containing products (4% or 6.9 million prescriptions) as compared to other opioid analgesics analyzed: extended-release oxycodone (10% or 3.9 million prescriptions), immediate-release oxycodone (9% or 4.8 million prescriptions), extended-release morphine (15% or 3.9 million prescriptions), immediate-release morphine (12% or 863,000 prescriptions) and hydromorphone (5% or 547,000 prescriptions).

In general, we observed similar prescribing patterns for combination hydrocodone-containing products and combination oxycodone-containing products during the time period examined.

4.7 Average days of Therapy per Prescription

Figure 4 in Appendix 2 shows the average days of therapy per prescription for combination hydrocodone-containing products as compared to various other opioid analgesics for year 2011. The average days of therapy for both combination hydrocodone-containing and combination oxycodone-containing prescriptions was approximately 14 days per prescription. Comparatively, the average days of therapy per prescription for extended-release formulations was higher with approximately 27 days for single-ingredient extended-release oxycodone and approximately 28 days for extended-release morphine. The average days of therapy per prescription for single-ingredient immediate-release oxycodone were approximately 22 days and approximately 18 days for immediate-release morphine. The average days of therapy per hydromorphone prescription was approximately 17 days.

4.8 Duration of Use Analysis

Table 4 in Appendix 2 shows the median and mean duration of therapy in days for combination hydrocodone-containing , combination oxycodone-containing, single-ingredient, immediate-release oxycodone, and single-ingredient, extended-release oxycodone prescription claims in an <u>unprojected</u> patient sample for years 2010 through 2011, cumulative. The <u>median</u> episode duration for combination hydrocodone-containing products, combination oxycodone-containing products, immediate-release oxycodone, and extended-release oxycodone were 8 days, 6 days, 19 days, and 31 days, respectively. The <u>mean</u> episode duration for combination hydrocodone-containing products, combination oxycodone-containing products, immediate-release oxycodone, and extended-release oxycodone were 45 days, 30 days, 72 days, and 43 days, respectively.

In addition, we examined the minimum and maximum days of therapy for patients with combination hydrocodone-containing products, combination oxycodone-containing products, immediate-release oxycodone, and extended-release oxycodone therapy to determine the estimated proportion of patients with therapy duration for each agent. Based on the minimum and the maximum therapy duration, patients were divided into 10 equal groups or deciles. Approximately 70% of patients with combination hydrocodone-containing product prescriptions claims had therapy duration of 16 days or less. We estimate that approximately 20% of the patient sample used combination hydrocodone-containing products for 32 days or longer. Approximately 70% of patients with combination oxycodone-containing product prescription claims had therapy duration of 12 days or less. We estimate that approximately 20% of the patient sample used combination oxycodone-containing products for 23 days or longer. Approximately 70% of patients with immediate-release oxycodone prescription claims had therapy duration of 31 days or less. We estimate that approximately 20% of the patient sample used immediate-release oxycodone agents for 93 days or longer. Approximately 60% of patients with extended-release oxycodone prescription claims had therapy duration of 31 days or less. We estimate that approximately 10% of the patient sample used extended-release oxycodone agents for 100 days or longer.

4.9 INDICATIONS FOR USE

Table 5 in Appendix 2 shows the most common diagnoses associated with the use of combination hydrocodone-containing products as compared to combination oxycodone-containing products, single-ingredient, extended-release oxycodone, single-ingredient, immediate-release oxycodone, extended-release morphine, immediate-release morphine, and hydromorphone. The number of drug use mentions[6] for hydromorphone and extended release oxycodone from office-based physician visits was below the acceptable count allowable to provide a reliable estimate of national use. Over the cumulative time period from year 2007 through 2011, “Diseases of the Musculoskeletal System and Connective Tissue” (ICD-9 codes 710-739) were the most common diagnoses associated with the use of all opioid analgesics analyzed; with approximately 25% of the total drug use mentions for combination hydrocodone-containing products, 20% of drug use mentions for combination oxycodone-containing products, 41% of drug use mentions for immediate-release oxycodone, 68% of drug use mentions for extended-release morphine, and 56% of drug use mentions for immediate-release morphine.

The second most common diagnoses associated with the use of combination hydrocodone-containing products was “Diseases of Respiratory System” (ICD-9 codes 462-493), with approximately 21% of the total drug use mentions followed by “Fractures, Sprains, Contusions and Injuries” (ICD-9 codes 800-999) with approximately 19% of the total drug use mentions. Similar patterns were observed for combination oxycodone-containing products in terms of diagnoses, with the only difference observed for conditions associated with “Diseases of Respiratory System” (ICD-9 codes 462-493), likely due to the antitussive indication of some combination hydrocodone-containing products.

[6] Encuity Research, LLC., uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

5 DISCUSSION

Throughout the time examined, the weight in kilograms sold of combination hydrocodone-containing products has been the market lead when compared to the other selected opioids analyzed. During year 2011 approximately 131 million analgesic combination hydrocodone-containing prescriptions were dispensed as compared to 5.3 million antitussive combination hydrocodone-containing prescriptions dispensed through U.S. outpatient retail pharmacies. During year 2011, approximately 47.1 million patients received dispensed prescriptions for combination hydrocodone-containing prescriptions followed by 15.1 million patients receiving dispensed prescriptions for combination oxycodone-containing prescriptions. Prescribing patterns for combination hydrocodone-containing products and combination oxycodone-containing products were very similar.

The greatest proportion of drug use mentions for combination hydrocodone-containing products was associated with the use of "Diseases of the Musculoskeletal System and Connective Tissue" (ICD-9 codes 710-739) followed by "Diseases of Respiratory System" (ICD-9 codes 462-493), and "Fractures, Sprains, Contusions and Injuries" (ICD-9 codes 800-999). Similar patterns were observed for combination oxycodone-containing products in terms of diagnoses, with the only difference observed for conditions associated with "Diseases of Respiratory System" (ICD-9 codes 462-493), likely due to the antitussive indication of some combination hydrocodone-containing products.

Furthermore, our analysis of average days of therapy per dispensed prescription as well duration of therapy analysis showed that combination hydrocodone-containing products and combination oxycodone-containing products were used for shorter time period (about 14 days) as compared to extended-release oxycodone (about 27 days) and extended-release morphine prescriptions (about 28 days).

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that combination hydrocodone-containing products are distributed primarily to the outpatient setting. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

We focused our analysis on only the outpatient retail pharmacy setting, therefore these estimates may not apply to other settings of care in which these products are used (e.g. mail-order/specialty pharmacy, and non-retail pharmacies). The estimates provided are national estimates, but no statistical tests were performed to determine statistical significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

Data from Source Healthcare Analytics' ProMetis Lx® provides *unprojected* patient counts with a prescription claim for selected opioids. Due to the sample size and the unreported pharmacy information, there are limitations in the ability to identify national trends in the data. In addition, the universe of mail order and specialty pharmacies contributing to these data are unknown.

Duration of therapy counts are based on the sample data only; therefore, they are not projected to national estimates.

Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly if use is not common in the pediatric population. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for the products in clinical practice. Encuity Research, LLC., recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

6 CONCLUSIONS

In year 2011, approximately 131 million prescriptions were dispensed and 47.1 million patients received a dispensed prescription for combination hydrocodone-containing analgesic products. Similar to combination oxycodone-containing products, combination hydrocodone-containing products had an average 14 days of therapy and were most commonly prescribed by General Practice/Family Medicine/Doctor of Osteopathy and Internal Medicine specialists and were used for conditions associated “Diseases of the Musculoskeletal System and Connective Tissue” (ICD-9 codes 710-739) followed by “Diseases of Respiratory System” (ICD-9 codes 462-493), and “Fractures, Sprains, Contusions and Injuries” (ICD-9 codes 800-999).

APPENDIX 1: TABLES AND FIGURES

FIGURE 1.

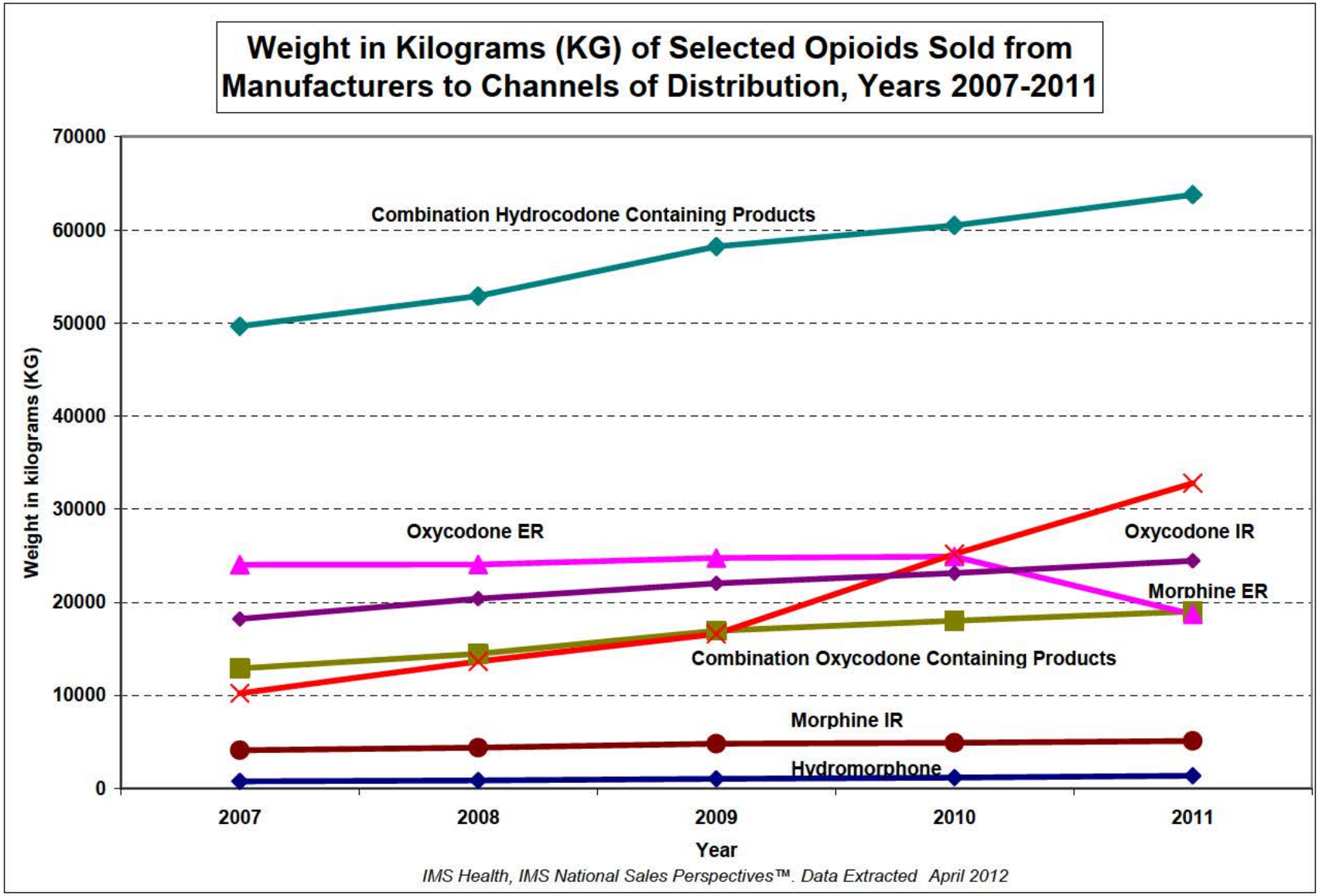

FIGURE 2.

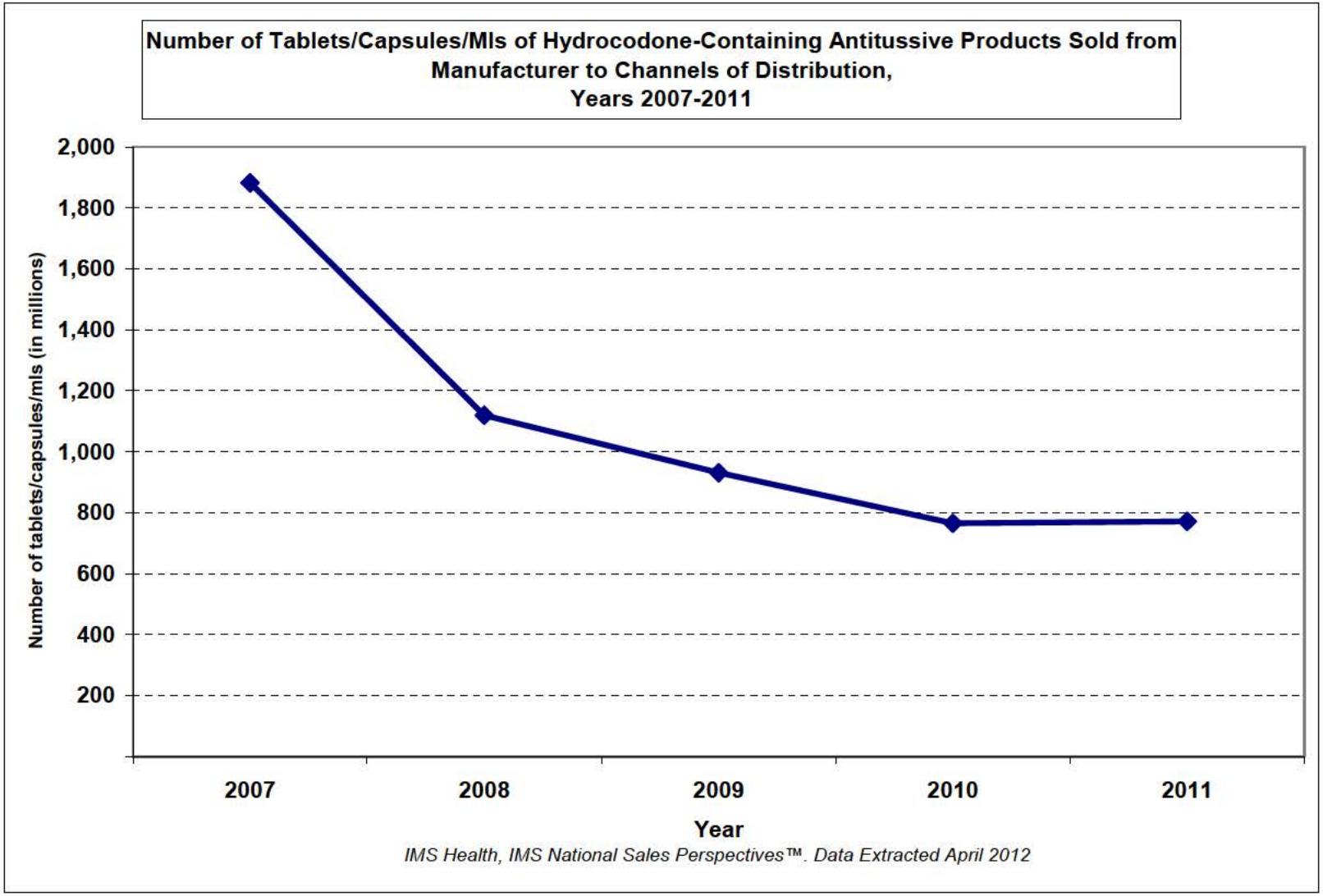
Number of Tablets/Capsules/Mls of Hydrocodone-Containing Antitussive Products Sold from Manufacturer to Channels of Distribution, Years 2007-2011
Number of tablets/capsules/mls (in millions)
2,000
1,800
1,600
1,400
1,200
1,000
800
600
400
200
2007
2008
2009
2010
2011
Year
IMS Health, IMS National Sales Perspectives™. Data Extracted April 2012

TABLE 1

Nationally Estimated Number of Prescriptions for Combination Hydrocodone-Containing Products, Stratified as Analgesics and Antitussives, Dispensed from U.S. Outpatient Retail Pharmacies for years 2007 through 2011

	2007		2008		2009		2010		2011	
	TRxs N	*Share %*	TRxs N	*Share %*	TRxs N	*Share %*	TRxs N	*Share %*	TRxs N	*Share %*
TOTAL MARKET	132,718,152	*100.0%*	133,322,635	*100.0%*	129,925,065	*100.0%*	130,855,251	*100.0%*	135,985,813	*100.0%*
Hydrocodone Analgesic Products	**120,558,365**	***90.8%***	**124,638,176**	***93.5%***	**123,785,711**	***95.3%***	**125,749,238**	***96.1%***	**130,704,028**	***96.1%***
Hydrocodone Antitussive Products	12,159,786	*9.2%*	8,684,459	*6.5%*	6,139,354	*4.7%*	5,106,013	*3.9%*	5,281,785	*3.9%*

Source: IMS Health, Vector One®: National. Data Extracted 9-12-12. File: VONA 2009-2039 Hydrocodone Products Analgesics and Cough Cold 9-12-12.xls

TABLE 2

Nationally Estimated Number of Combination Hydrocodone-Containing and Comparators (Oxycodone ER/IR, Combination oxycodone-containing, Morphine ER/IR, and Hydromorphone) Prescriptions Dispensed Through U.S. Outpatient Retail Pharmacies, Years 2007-2011

	2007		2008		2009		2010		2011	
	TRx	*Share %*	TRx	*Share %*	TRx	*Share %*	TRx	*Share %*	TRx	*Share %*
Total Market	**171,193,887**	***100.0%***	**180,024,122**	***100.0%***	**181,834,902**	***100.0%***	**189,517,906**	***100.0%***	**198,092,751**	***100.0%***
Hydrocodone Analgesic Products	**120,558,352**	***70.4%***	**124,638,107**	***69.2%***	**123,785,684**	***68.1%***	**125,749,235**	***66.4%***	**130,704,029**	***66.0%***
Hydrocodone/Acetaminophen	118,074,137	97.9%	122,260,964	98.1%	121,575,144	98.2%	123,556,210	98.3%	128,546,058	98.3%
Hydrocodone/Ibuprofen	2,484,184	2.1%	2,377,134	1.9%	2,210,530	1.8%	2,193,014	1.7%	2,157,965	1.7%
Hydrocodone/Aspirin	31	0.0%	9	0.0%	10	0.0%	11	0.0%	6	0.0%
Total Oxycodone	43,405,133	*25.4%*	47,225,509	*26.2%*	49,419,388	*27.2%*	54,365,207	*28.7%*	56,983,248	*28.8%*
Oxycodone Combination	28,803,782	*66.4%*	30,805,888	*65.2%*	32,239,395	*65.2%*	33,704,239	*62.0%*	34,653,743	*60.8%*
Oxycodone/Acetaminophen	28,545,736	*99.1%*	30,596,686	*99.3%*	32,074,676	*99.5%*	33,569,445	*99.6%*	34,545,056	*99.7%*
Oxycodone/Aspirin	206,142	*0.7%*	179,246	*0.6%*	144,547	*0.4%*	120,401	*0.4%*	99,233	*0.3%*
Oxycodone/Ibuprofen	51,904	*0.2%*	29,956	*0.1%*	20,172	*0.1%*	14,393	*0.0%*	9,454	*0.0%*
Oxycodone Single Ingredient	14,601,351	*33.6%*	16,419,621	*34.8%*	17,179,993	*34.8%*	20,660,968	*38.0%*	22,329,505	*39.2%*
Oxycodone Immediate Release	6,304,442	*43.2%*	8,093,643	*49.3%*	9,134,757	*53.1%*	13,190,814	*63.7%*	16,591,561	*74.3%*
Oxycodone Extended Release	8,296,909	*56.8%*	8,325,977	*50.7%*	8,045,237	*46.8%*	7,470,153	*36.2%*	5,737,943	*25.7%*
Morphine Sulfate	5,581,911	*3.3%*	6,299,627	*3.5%*	6,463,446	*3.6%*	6,981,624	*3.7%*	7,635,623	*3.9%*
Morphine ER	4,236,471	*75.9%*	4,822,350	*76.5%*	5,104,791	*79.0%*	5,619,457	*80.5%*	6,053,915	*79.3%*
Morphine IR	1,345,440	*24.1%*	1,477,276	*23.5%*	1,358,655	*21.0%*	1,362,166	*19.5%*	1,581,708	*20.7%*
Hydromorphone	1,618,707	*0.9%*	1,833,332	*1.0%*	2,135,612	*1.2%*	2,387,752	*1.3%*	2,735,846	*1.4%*

Source: IMS, Vector One®: National (VONA), extracted 09/ 2012, Source Files: VONA_2012-2002_Hydrocodone,_oxycodone,_morphine,_hydromorphone_09-20-12(1).xls; VONA_2012-1613_Oxycodone_forms_09-20-12(1).xls; VONA_2012-1613_Morphine_IR_and_ER_09-20-12(1).xls

FIGURE 3

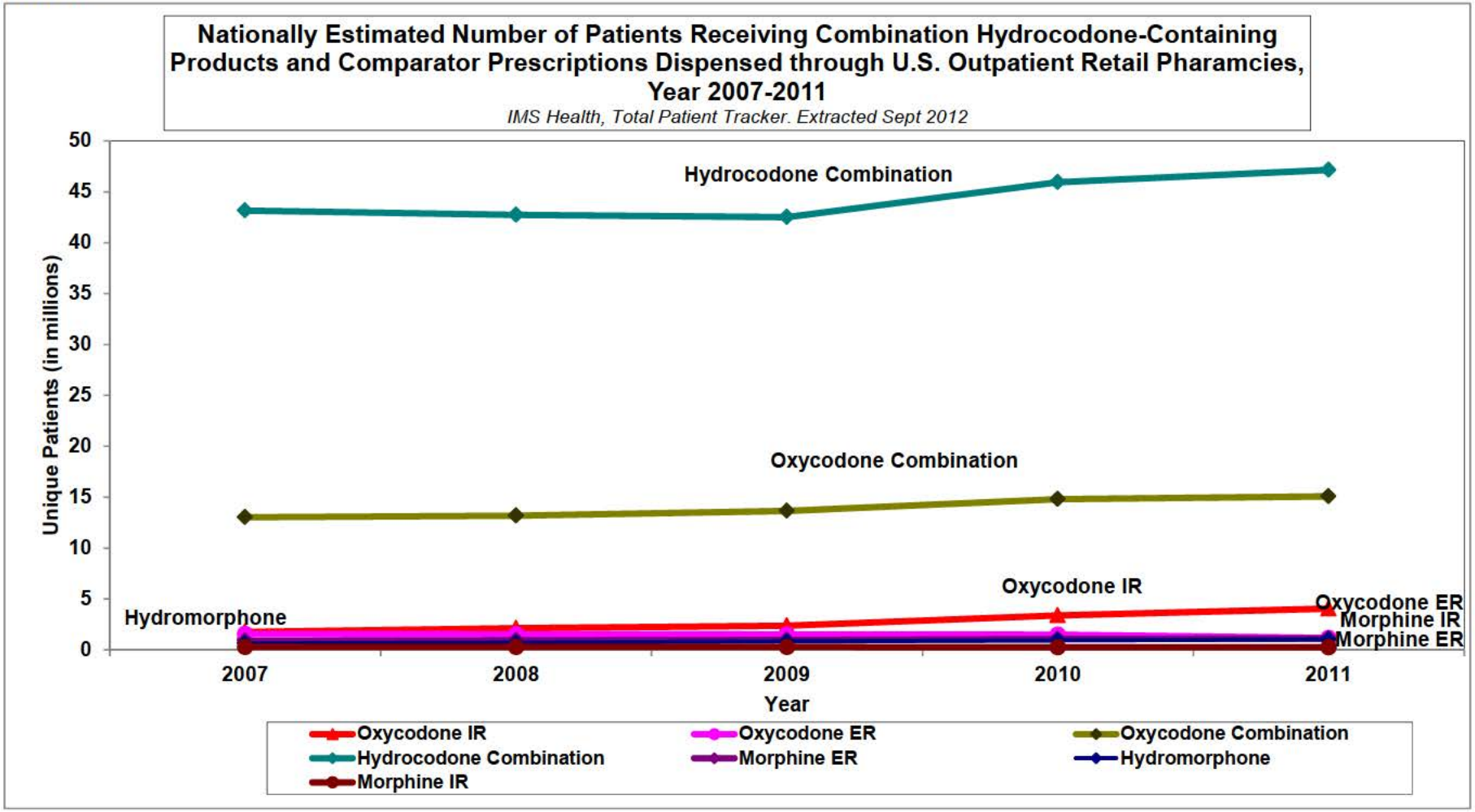
Nationally Estimated Number of Patients Receiving Combination Hydrocodone-Containing Products and Comparator Prescriptions Dispensed through U.S. Outpatient Retail Pharamcies, Year 2007-2011
IMS Health, Total Patient Tracker. Extracted Sept 2012
Unique Patients (in millions)
50
45
40
35
30
25
20
15
10
5
0
Hydrocodone Combination
Oxycodone Combination
Oxycodone IR
Oxycodone ER
Morphine IR
Morphine ER
Hydromorphone
2007
2008
2009
2010
2011
Year
Oxycodone IR
Oxycodone ER
Oxycodone Combination
Hydrocodone Combination
Morphine ER
Hydromorphone
Morphine IR

TABLE 3

Number of Prescriptions Dispensed for Selected Opioids by Top Prescribing Specialties Through U.S. Outpatient Retail Pharmacies, Years 2007-2011 cumulative

	Hydrocodone Combination		Oxycodone Combination		Oxycodone IR		Oxycodone ER		Morphine IR		Morphine ER		Hydromorphone	
	TRx	*Share %*	TRx	*Share %*	TRx	*Share %*	TRx	*Share %*	TRx	*Share %*	TRx	*Share %*	TRx	*Share %*
General Practice/Family Practice/Osteopathy	160,181,555	*25.6%*	29,961,318	*18.7%*	12,436,964	*23.3%*	10,133,854	*26.8%*	1,790,752	*25.1%*	6,374,048	*24.7%*	1,829,683	*17.3%*
Internal Medicine	87,793,125	*14.0%*	20,013,405	*12.5%*	7,911,481	*14.8%*	6,399,322	*16.9%*	1,268,562	*17.8%*	3,860,351	*14.9%*	1,552,896	*14.7%*
Orthopedic Surgery	51,929,989	*8.3%*	14,248,303	*8.9%*	2,352,884	*4.4%*	1,534,447	*4.1%*	49,483	*0.7%*	312,570	*1.2%*	546,514	*5.2%*
Unspecified	35,074,830	*5.6%*	9,389,016	*5.9%*	4,344,635	*8.1%*	2,332,718	*6.2%*	516,725	*7.3%*	1,864,053	*7.2%*	720,932	*6.8%*
Physician Assistant	24,076,466	*3.8%*	8,007,884	*5.0%*	2,617,768	*4.9%*	1,440,433	*3.8%*	225,019	*3.2%*	1,186,162	*4.6%*	527,334	*5.0%*
Nurse Practitioner	20,914,534	*3.3%*	5,748,315	*3.6%*	2,993,887	*5.6%*	1,875,406	*5.0%*	384,056	*5.4%*	1,736,995	*6.7%*	462,020	*4.4%*
Dentist	64,867,932	*10.4%*	8,568,981	*5.3%*	178,467	*0.3%*	50,349	*0.1%*	8,073	*0.1%*	23,529	*0.1%*	48,238	*0.5%*
Anesthesiologists	16,299,925	*2.6%*	6,863,668	*4.3%*	4,831,093	*9.1%*	3,888,158	*10.3%*	863,447	*12.1%*	3,944,589	*15.3%*	546,514	*5.2%*
All Others	164,297,047	*26.4%*	57,406,156	*35.8%*	15,647,914	*29.3%*	10,221,531	*27.0%*	2,019,129	*28.3%*	6,534,687	*25.3%*	4,360,474	*41.2%*

Source: IMS, Vector One®: National (VONA) Extracted September 2012. Source File: VONA 2012-1613 Morphine IR and ER by Specialty 9-25-12.xls; VONA 2012-1613 Morphine IR and ER by Specialty 9-25-12.xls; VONA_2012-1613_hydromorphone_specialties_09-25-12(1).xls; VONA_2012-1613_Oxycodone_Combo_Specialties_09-25-12(1).xls; VONA_2012-1613_Hydrocodone_Specialties_09-25-12(1).xls

FIGURE 4.

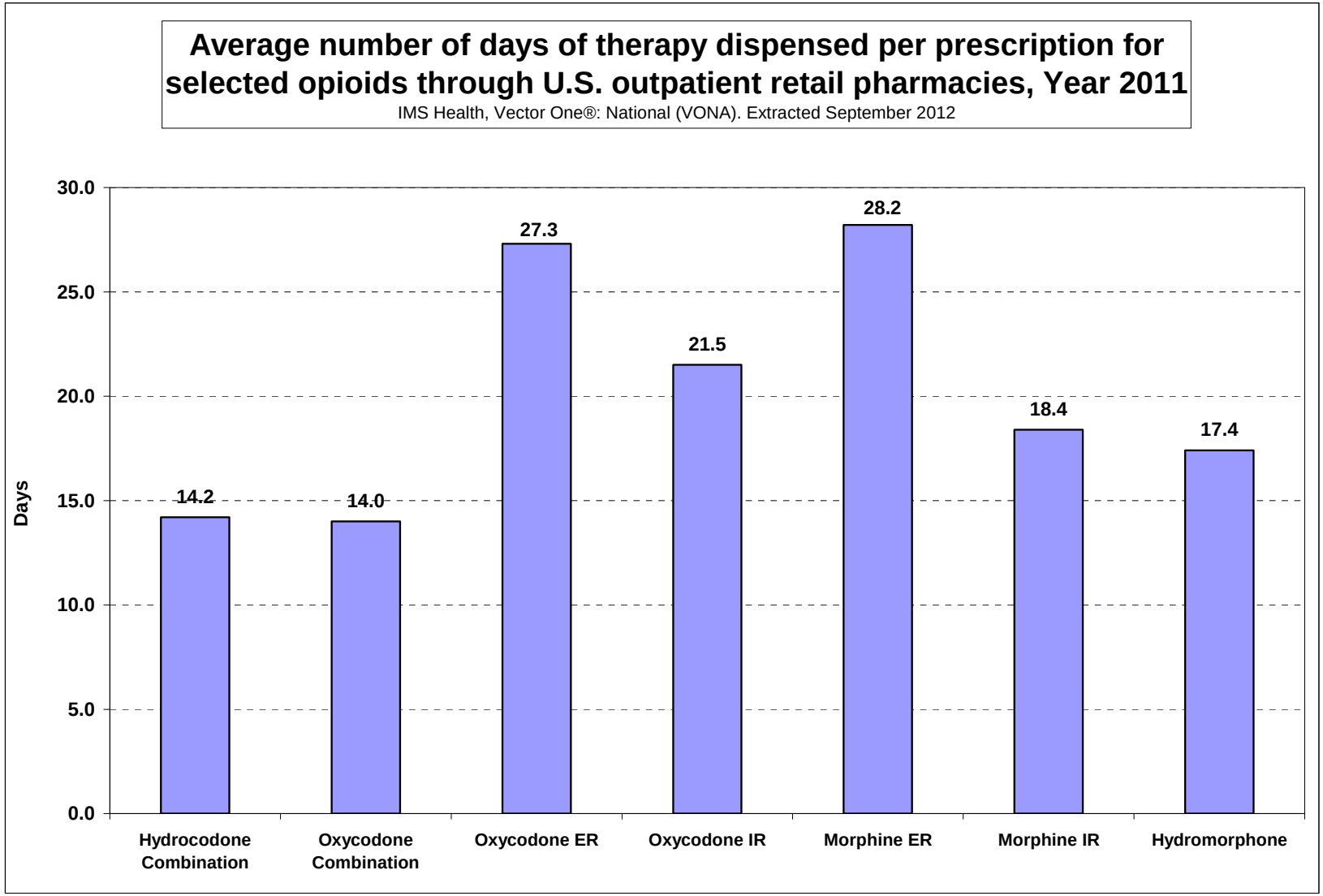
Average number of days of therapy dispensed per prescription for selected opioids through U.S. outpatient retail pharmacies, Year 2011
IMS Health, Vector One®: National (VONA). Extracted September 2012
Days
30.0
25.0
20.0
15.0
10.0
5.0
0.0
14.2
14.0
27.3
21.5
28.2
18.4
17.4
Hydrocodone Combination
Oxycodone Combination
Oxycodone ER
Oxycodone IR
Morphine ER
Morphine IR
Hydromorphone

TABLE 4.

Crude days of therapy for selected opioids in a sample of patients
Cumulative January 2010 through December 2011

Regimen	Number of sample patients	Days of Therapy			
		Median	Average	Min	Max
HYDROCODONE COMBO	16,281,353	8	45.1	2	730
OXYCODONE COMBO	5,497,455	6	30.0	2	730
OXYCODONE IR	1,168,258	19	72.4	2	730
OXYCODONE ER	70,654	31	42.6	2	664

Source: Source Healthcare Analytics ProMetis Lx®, January 2010-December 2011, extracted January, 2011,
Source File: SHACPA 2009-2039 Hydrocodone Deciles 01-31-12.xls

Estimated Duration of Therapy by Deciles for a Sample of Patients on Hydrocodone Combination Products, Oxycodone Combination Products, Oxycodone ER, Oxycodone IR, January 01, 2010 through December 31, 2011 cumulative

Regimen	Number of sample patients	DECILES									
		1	2	3	4	5	6	7	8	9	10
HYDROCODONE COMBO	16,281,353	2 - 3	3 - 4	4 - 5	5 - 6	6 - 8	8 - 11	11 - 16	16 - 32	32 - 109	109 - 730
OXYCODONE COMBO	5,497,455	2 - 3	3 - 4	4 - 5	5 - 6	6 - 6	6 - 8	8 - 12	12 - 23	23 - 59	59 - 730
OXYCODONE IR	1,168,258	2 - 4	4 - 6	6 - 8	8 - 11	11 - 19	19 - 31	31 - 47	47 - 93	93 - 221	221 - 730
OXYCODONE ER	70,654	2 - 6	6 - 10	10 - 16	16 - 23	23 - 31	31 - 31	31 - 37	37 - 62	62 - 100	100 - 664

Source: Source Healthcare Analytics ProMetis Lx® , January 2010-December 2011, extracted January, 2011, Source File: SHACPA 2009-2039 Hydrocodone Deciles 01-31-12.xls

TABLE 5.

Diagnoses Associated with Use (by grouped ICD-9 codes) for Selected Opioids as Reported by Office-Based Physicians in the U.S., Jan 2007-Nov 2011 cumulative										
	Hydrocodone Combo		Oxycodone Combo		Oxycodone IR		Morphine ER		Morphine IR	
	N(000)	%	N(000)	%	N(000)	%	N(000)	%	N(000)	%
Total Market	**2,850**	***100%***	**1,406**	***100%***	**566**	***100%***	**2,618**	***100%***	**407**	***100%***
Diseases of the Musculoskeletal System and Connective Tissue (710-739)	699	*25%*	287	*20%*	230	*41%*	1,781	*68%*	226	*56%*
Disease of Respiratory System (462-493)	594	*21%*	31	*2%*						
Fractures, Sprains, Contusions, Injuries (800-999)	547	*19%*	368	*26%*	43	*8%*	89	*3%*	15	*4%*
All others	360	*13%*	102	*7%*	13	*2%*	64	*2%*	27	*7%*
Follow up examinations	286	*10%*	198	*14%*	11	*2%*	113	*4%*	21	*5%*
Headaches and Nerve Pain (337-359)	98	*3%*	51	*4%*	213	*38%*	392	*15%*	81	*20%*
Fever and General Symptoms (780-789)	96	*3%*	53	*4%*	28	*5%*	64	*2%*	25	*6%*
Neoplasms (140-239)	70	*2%*	5	*0%*	31	*5%*	102	*4%*	2	*0%*
Disease of Genitourinary System (592-626)	62	*2%*	311	*22%*			11	*0%*	9	*2%*
Bacterial, Viral and Parasitic Infections (001-138)	39	*1%*	4	*0%*	1	*0%*	8	*0%*	2	*0%*

Encuity Research LLC. Physician Drug and Diagnosis Audit, Jan07-Nov11. Extracted January 2012, Source Files: PDDA 2009-2039 Hydrocodone, oxycodone, morphine, hydromorphone DX4 (new grouping) 01-20-12.xls; PDDA 2009-2039 Oxycodone DX4 01-20-12(2).xls; PDDA 2009-2039 Morphine DX4 01-20-12(1).xls

APPENDIX B: DRUG USE DATABASE DESCRIPTIONS

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.

IMS Vector One®: National (VONA)

The IMS, Vector One®: National (VONA) database 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 sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

IMS Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

Source Healthcare Analytics' ProMetis Lx®

The Source Healthcare Analytics' ProMetis Lx® database is a longitudinal patient data source which captures adjudicated prescription claims across the United States across all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The database contains approximately 4.8 billion prescriptions claims linked to over 190 million unique prescription patients, of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents nearly 30,000 pharmacies, 1,000 hospitals, 800 outpatient facilities, and 80,000 physician practices.

Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA)

Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns. Encuity Research, LLC., uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS
10903 New Hampshire Ave., Silver Spring, MD 20993 • Tel: (301)796-2280

Response to Request for Consultation

Date: March 15, 2007

To: Corinne P Moody
Science Policy Analyst
Controlled Substance Staff, HFD-009

From: Jin Chen, M.D., Ph.D.
Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Sharon Hertz, M.D.
Rigoberto Roca, M.D.
Deputy Directors
Division of Anesthesia, Analgesia and Rheumatology Products

Bob Rappaport, M.D.
Division Director
Division of Anesthesia, Analgesia and Rheumatology Products

Re: CSS Consult on the role of hydrocodone/acetaminophen combination products in the therapeutic armamentarium
Related to: ANDA 88-058 (Vicodin), ANDA 40-288 (Zydone), ANDA 40-100 (Lortab), etc.

EXECUTIVE SUMMARY

1. The hydrocodone/acetaminophen combination products are the most commonly used products among opioid analgesics for management of non-cancer pain and are widely used for cancer pain as well.[i] (Verispan, PDDA, Years 2002 – 2005, Extracted December 2006).

[i] Kendra Worthy: Drug Use Review of Acetaminophen (APAP)/Hydrocodone. OSE Review, Jan 23, 2007

2. The most common diagnoses for which they are prescribed are surgical pain, backache/lumbago, and joint pain/osteoarthritis (Verispan, PDDA, Years 2002 – 2005, Extracted December 2006).

3. There are limited alternate analgesic options for physicians treating pain under Schedule III or Schedule IV of the Controlled Substance Act, or that are unscheduled. Most alternatives are opioids under Schedule II which cannot be prescribed with refills. Re-scheduling the hydrocodone/acetaminophen combination products from Schedule III to Schedule II will likely negatively impact patient access to this product, and may result in increased use of other Schedule II opioids.

4. There are data that suggest that opioid/acetaminophen combination products are associated with acetaminophen overdose, hepatotoxicity or death. Hydrocodone/acetaminophen combination products are on top of the list of opioid/acetaminophen combination products associated with acetaminophen toxicity.

BACKGROUND

The Controlled Substances Staff (CSS) has received a request for an 8-factor analysis of the abuse liability of hydrocodone combination products from the Drug Enforcement Administration (DEA). A citizen's petition was submitted to DEA by (b) (6) , M.D., requesting the rescheduling of hydrocodone combination products from Schedule III to Schedule II of the Controlled Substances Act (CSA). The DEA has requested that FDA provide "*a scientific and medical evaluation and a scheduling recommendation from the Department of Health and Human Service in order that this agency may reach its final determination on the petition to reschedule hydrocodone combination products*".

CSS has requested a consultation by the division seeking information on the role of hydrocodone/acetaminophen (acetaminophen) combination products in the therapeutic armamentarium. Five questions were provided to assist with the consult request.

RESPONSE TO CSS's QUESTIONS

CSS Question #1. *What is the role of these products in the management of pain?*

DAARP Response: The labeled indication for the combination of hydrocodone and acetaminophen is for the relief of moderate to moderately severe pain. The hydrocodone/acetaminophen combination products are the most commonly prescribed opioid products for the management of acute pain and chronic pain, including cancer and non-cancer pain. These products are used on an intermittent basis as well as on a

continuous, daily basis. In the *Guideline for the Management of Cancer Pain in Adults and Children*[1], hydrocodone/acetaminophen combination products are recommended for management of mild, moderate and severe pain associated with cancer in adults and children and are considered a Step 2 therapeutic option on the World Health Organization Analgesic Ladder[2]. Based on a review of prescribing patterns from the Verispan, Physician Drug and Diagnosis Audit (PDDA), hydrocodone/acetaminophen combinations are the most commonly used products among opioid analgesics for management of non-cancer pain as well[ii] (Verispan, PDDA, Years 2002 – 2005, Extracted December 2006).

Based on projected dispensed prescription data from the Verispan, Vector One®: National (VONA) audit, the four most commonly dispensed outpatient prescriptions of opioid/acetaminophen combination products from 2002 to 2005 were hydrocodone, oxycodone, propoxyphene and codeine with the hydrocodone combinations accounting for 60% of the market share for opioid/acetaminophen combinations in 2005[i] (Verispan, VONA, Years 2002 – 2005, Extracted January 2007) Just over 98% of the hydrocodone prescriptions were dispensed as acetaminophen combinations. There are no single entity, hydrocodone-alone products approved for pain management in the U.S., although there are combination products of hydrocodone for pain that contain either ibuprofen or aspirin.

The number of dispensed prescriptions for all of the opioid/acetaminophen combination products increased from 2002 to 2005 by 12% (155 to 173 million) and by 21% for hydrocodone/acetaminophen combination products (86 to 104 million). Hydrocodone/acetaminophen combination products have been at the top of list since 1997 [i] (Verispan, VONA, Years 1996 – 2005, Extracted November 2007) and in the past four years the market share has increased from 56% in 2002 to 60% in 2005 (Verispan, VONA, Years 2002 – 2005, Extracted January 2007).

CSS Question #2. *What are they usually prescribed for?*

DAARP Response: The approved indication for hydrocodone/acetaminophen combination products is *for the relief of moderate to moderately severe pain.*

As described in the Hydrocodone/Acetaminophen monograph in the Clinical Pharmacology Online database[iii], the products have been prescribed for severe pain due to cancer, dental pain, headache, migraine, back pain, bone pain, arthralgia and myalgia with maximum daily dose of 4 g acetaminophen and 60 mg hydrocodone. The recently published *Opioid Guidelines in the Management of Chronic Non-Cancer Pain* indicates that opioids are extensively used in managing chronic pain, although there is limited supportive efficacy and safety evidence[3]. The guideline states that as many as 90% of

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[ii] Kendra Worthy: Drug Use Review of Acetaminophen (APAP)/Hydrocodone. OSE Review, Jan 23, 2007

[iii] Clinical Pharmacology monographs at http://www.clinicalpharmacology-ip.com/ are developed through an independent, peer-reviewed process and represent an objective analysis of clinically-relevant drug information (http://www.clinicalpharmacology.com/marketing/editorial_policy.html).

patients have been reported to receive an opioid analgesic for chronic pain in pain management settings. As per this guideline, hydrocodone in combination with acetaminophen or ibuprofen is the most commonly used opioid for the treatment of chronic pain.

Dispensed prescription data from Verispan, Vector One®: National (VONA) retail pharmacy audit reveals that hydrocodone/acetaminophen products are prescribed most often by general practioners, internists, dentists and orthopedic surgeons, followed by emergency medicine physicians, general surgeons and anesthesiologists[i] (Verispan, VONA, Years 2002 – 2005, Extracted November 2007). A review of physician prescribing patterns from the Verispan, Physician Drug and Diagnosis Audit (PDDA) reveals that the most common diagnoses for which they are prescribed are surgical pain, backache/lumbago, and joint pain/osteoarthritis (Verispan, PDDA, Years 2002 – 2005, Extracted December 2006).

CSS Question #3. *What will be the impact if they are rescheduled from III to II?*

DAARP Response: One hypothesis for the more frequent use of hydrocodone/acetaminophen combination products as compared to other opioid analgesics is the relative ease of prescribing Schedule III products as compared to Schedule II products, particularly that the former allows for refills to be written with the initial prescription. The re-scheduling from Schedule III to Schedule II will likely negatively impact patient access to this product. Patients with chronic pain will be the most negatively impacted.

There are limited alternate choices for physicians under Schedule III. Codeine in combination with acetaminophen or aspirin is not as frequently prescribed as hydrocodone combinations, likely due to less efficacy and more adverse events such as nausea and constipation, although there are little data to quantify these effects. Codeine requires metabolism by the cytochrome P450 enzyme, 2D6, to its active metabolite, morphine. As many as 7% of the general U.S. population lacks adequate 2D6 levels for this metabolic activity. Also under Schedule III is morphine in combination, but there are no such products approved in the U.S. Analgesics under Schedule IV such as butorphanol, dextropropoxyphene, and pentazocine, and unscheduled products such as tramadol, are generally recognized to be less effective for moderate to severe pain than hydrocodone and the Schedule II opioids. While there may be some increase in use of these products, there is likely to be an increase in use of the Schedule II opioids as a result of rescheduling the hydrocodone/acetaminophen combinations. Many of the currently marketed immediate-release opioids, including all of the immediate-release morphines and many of the immediate-release oxycodones, are unapproved products. There are approved oxycodone/acetaminophen combination products (Percocet, Tylox), which may increase in frequency of use if the hydrocodone/acetaminophen combination products become Schedule II. There may also be an increase in use of the nonsteroidal anti-inflammatory drugs, although they are generally not sufficient for severe acute postoperative pain and are considered as the first step in analgesic therapy for chronic

pain, to be followed by opioids, alone or in combination, when greater analgesia is needed.

Another consequence of a scheduling change may be greater use of other hydrocodone products which may remain under Schedule III. These include the analgesic combinations of hydrocodone and ibuprofen which are currently approved for the short-term (generally less than 10 days) management of acute pain, and hydrocodone and aspirin. It is possible that there could also be off-label use of some of the hydrocodone combination products approved for cough suppression such as Hycodan, a tablet formulation of hydrocodone 5 mg with a low dose of homatropine (1.5 mg) intended to discourage deliberate overdosage.

CSS Question #4. *Is there evidence that each component adds to the efficacy of the treatment?*

DAARP Response: The hydrocodone/acetaminophen combination products were approved under 505(j), based in part on therapeutic equivalence with codeine.

Pharmacologically, hydrocodone and acetaminophen mediate analgesic effects through different mechanisms of action. Hydrocodone is a mu opioid receptor agonist, a centrally acting analgesic believed to change the perception of pain at the level of the spinal cord and higher in the CNS, as well as alter the emotional response to painful stimuli[3]. Acetaminophen may also be a centrally acting analgesic although its analgesia mechanism of action is not completely understood. Recent studies suggest acetaminophen selectively inhibits the peroxidase active site of COX-1 and COX-2 (or prostaglandin H2 synthases 1 and 2, PGHS 1 and 2) in neurons and vascular endothelial cells but not in platelets and inflammatory cells[4]. This cellular selectivity of COX inhibition results in analgesic and antipyretic effects of acetaminophen with little anti-platelet and anti-inflammatory activities.

The rationale for combination analgesic products such as hydrocodone with acetaminophen includes: [5-8]

- Increased effects: additive or synergetic analgesic effects of the combination based on analgesia through different pharmacological mechanisms
- Decreased adverse reactions: the additive efficacy may permit use of lower doses of the individual components in the combination subsequently reducing the frequency or severity of dose-dependent adverse drug reactions
- Increased compliance: convenience of the combination product over taking the individual components separately. (Note, there is no approved product in the U.S. that contains hydrocodone alone).

The data available in the literature that assess the efficacy of the combination in comparison to the individual components are limited. Only four full factorial design studies of opioid/acetaminophen combinations were identified, one evaluating

hydrocodone/acetaminophen, one evaluation oxycodone/acetaminophen and two evaluating codeine/acetaminophen. There are a few partial factorial design studies, which compare the combination with acetaminophen alone. The literature suggests that the combination of codeine and acetaminophen results in an additive analgesic effect compared to the individual components. The study to evaluate the analgesic superiority of hydrocodone in combination with acetaminophen enrolled postpartum women in a randomized, double-blind, placebo-controlled, full factorial study[9]. The patients received a single oral dose of hydrocodone/acetaminophen (10/1000 mg) combination (n=21), hydrocodone (10 mg) (n=22), acetaminophen (1000 mg) (n=22) or placebo (n=22) followed by a 6-hour pain assessment. All treatments were statistically superior to placebo and the hydrocodone/acetaminophen combination product was noted to provide better pain relief as compared to hydrocodone or acetaminophen alone, but failed based on the assessment of the change in pain intensity change from baseline.

CSS Question #5. *What is the hepatotoxicity of the hydrocodone combination products in general?*

DAARP Response: The opioid/acetaminophen combination products, including the hydrocodone/acetaminophen combination products, have the same hepatotoxic profile as acetaminophen single-entity products. There is no data to suggest that the opioid in the combination increases the hepatotoxic effects of acetaminophen. However, opioid/acetaminophen combination products, particularly the hydrocodone/acetaminophen combination products, have contributed approximately half of the acute liver failure cases reported from 22 study centers in the U.S. between 1998 and 2003; most were related to unintentional acetaminophen overdose.

There are limited data in the literature from evaluations of the pharmacokinetic and pharmacodynamic interactions between opioids and acetaminophen that suggest a theoretical concern for enhanced hepatotoxicity from opioid/acetaminophen combination products. Several studies in animals have demonstrated that peripheral or central (intraventricular) administration of morphine, hydromorphone or propoxyphene depletes hepatocellular glutathione [10-14], presumably through stimulation of central mu-opiate receptors. Although hydrocodone was not administered in these studies, its active metabolite, hydromorphone, did have an effect on hepatic glutathione. The data suggests that depletion of hepatic glutathione may be a class effect of opioids. Glutathione is a key factor in the detoxification of NAPQI, (N-acetyl-p-benzoquinone imine), a hepatotoxic metabolite of acetaminophen. It is therefore possible, that glutathione depletion by opioids may enhance acetaminophen-induced hepatotoxicity or may decrease the hepatic threshold to acetaminophen toxicity. In contrast, one nonclinical study demonstrated that repeated exposure to incremental doses of acetaminophen in mice resulted in up-regulated glutathione levels and down-regulated hepatic enzymes, CYP2E1 and CYP1A2, with a 4-fold increase in LD50 in response to a subsequent lethal dose of acetaminophent[15]. This study suggests that chronic exposure of acetaminophen from opioid combinations may attenuate the opioid-induced hepatic glutathione depletion.

A recently published study (sponsored by Purdue Pharma LP) demonstrated that 1000 mg of acetaminophen in a combination with either oxycodone, hydromorphone or morphine, administered every six hours for 14 days, resulted in an increased serum ALT in healthy subjects, comparable to the effects of an acetaminophen-only control[16]. These results suggest that the opioid component does not increase hepatotoxicity more than that of acetaminophen alone.

While the combination of hydrocodone and acetaminophen was not evaluated in the above study, it was included in an unpublished study conducted by the same sponsor (Purdue Pharma LP) which was submitted to IND 55,965. In this study healthy adult subjects were treated with two tablets of Vicodin (hydrocodone/acetaminophen 5/500 mg), the study drug, or placebo every six hours for 14 days. Elevations in ALT (>3x ULN) during the study occurred in 45% of subjects who received Vicodin and 3% of subjects who received placebo. There was no acetaminophen-only treatment arm.

According to a report by the Acute Liver Failure Study Group in 2005[17], 275 (42%) of 662 confirmed acute liver failure (ALF) cases collected from 22 U.S. academic medical centers over a 6-year period (January 1, 1998 through December 31, 2003) were related to acetaminophen overdose.

Among the 275 APAP-related ALF cases:

- 48% (n=131) reported an unintentional overdose defined as "a multiple-timepoint ingestion to relieve pain or other somatic symptoms with denial of suicidal intent".
- 44% (n=122) were intentional (suicidal)
- 44% (n=120) took prescription APAP/narcotic combination products
    - 69% (83 of 120) were hydrocodone/APAP combination
    - 63% (83 of 131) were unintentional
    - 18% (22 of 122) were intentional

The authors pointed out that acetaminophen-related ALF cases were probably under-reported in the study due to the exclusion of those cases which lacked informed consent or adequate information to ensure the diagnosis. The 22 study sites represented approximately 30% of U.S. transplant capability and recorded an average of 49 acetaminophen-related ALF cases per year over the 6-year period. They estimated that at least 250 acetaminophen-related ALF cases per year were seen at U.S. transplant centers[17].

The authors noted several limitations to the study. They were unable to evaluate the presence of any associations between opioid tolerance and physical dependence with opioid/acetaminophen-related unintentional acetaminophen overdose. The study was unable to distinguish between unintentional overdose due to "known" overdose (acetaminophen overdose due to seeking more pain relief) and the "unknown" overdose (acetaminophen overdose due to mistaking multiple drugs containing acetaminophen). The report did not provide detailed exposure information on the opioid/acetaminophen

combination products in the ALF patients, such as duration of treatment, dosage, concurrent medications, clinical indication (acute or chronic pain), history of opioid or acetaminophen use and concomitant medical history (particularly liver disease). They also noted that more detailed comparisons between over-the-counter (OTC) and prescription products and acetaminophen-related ALF should be performed.

A review conducted by OSE[iv] using AERS and other databases suggest that both opioid/acetaminophen combination products and OTC acetaminophen products are associated with acetaminophen overdose, hepatotoxicity or death. Hydrocodone/acetaminophen combination products are on top of the list of opioid/acetaminophen combination products associated with acetaminophen toxicity. However, further analyses may be needed to assess the differences in these acetaminophen-related events between opioid/acetaminophen and OTC acetaminophen products and to estimate whether tolerance to and/or physical dependence on opioids and abuse/misuse of opioids play a critical role in the opioid/acetaminophen-related events.

APPENDICES

[iv] Chang YJ et al: OSE Safety Review: Acetaminophen, Hepatotoxicity, Overdose and Death. Feb 5, 2007

Appendix 1

Literature Summary Table of Efficacy Studies on Hydrocodone/acetaminophen Combination Products

Study Medication	Study Indication	Study Subject	Study Design	Efficacy	Safety	Publication
HC/acetaminophen (10/1000mg), HC (10mg), acetaminophen (1000mg), Codeine (60mg), Placebo	Acute pain, (postpartum)	N=108 patients (n=22/arm)	R/DB/PC single-dose, 6-hr pain assessment (hourly)	All Txs were superior in analgesia (PR, PI and 50%-responder) to placebo; HC/acetaminophen > HC or acetaminophen but only 50%-responder showed additive analgesia		Beaver 1980[8] ***Detailed review in Appendix 1-1***
HC/acetaminophen (7.5/500mg) OX/acetaminophen (5/325mg) OX/IB (5/400mg) placebo	Acute pain, (post-op dental pain); Single-dose	Total n=249 patients (62/arm)	R/DB/PC single-dose, 6-hr pain assessment (hourly)	Dropout rates (w/ LOCF): 18% (OX/IB), 49% (OX/acetaminophen), 74% (HC/acetaminophen) and 73% (PC) TOTPAR6 and SPID6: OX/IB>OX/acetaminophen=HC/acetaminophen >PC ($p<0.01$) Rescue medication (% pt) PC>HC/acetaminophen>OX/acetaminophen>OX/IB Time to rescue (short to long): OX/IB<OX/acetaminophen=HC/acetaminophen <placebo	Common AEs: nausea and vomiting; OX/acetaminophen >HC/acetaminophen>OX/IB >PC	Litkowski LJ et al, 2005[31]
HC/acetaminophen (7.5/750mg), Ketorolac (10mg), Placebo (6 hour then keto)	Acute pain, Ambulatory arthroscopic or laparoscopic tubal ligation; Single-dose & multiple-dose (q4-6h)	Total n=252 patients (82-87/arm)	R/DB, Assessment at single-dose phase (hourly x6 hrs) and at multiple-dose phase (daily x3 days)	Overall dropout rate: 70% (63 HC/AP, 70% keto, 77% PC) at 6-hr and 78% at day 3 6-hour analgesia in arthroscopy: HC/acetaminophen < ketorolac < placebo 6-hour analgesia in laparoscopic tubal ligation: no difference among 3 txs At end of days 1,2,3 no differences in analgesia among 3 txs.	Common AEs: nausea, vomiting and somnolence; HC/acetaminophen >Ketorolac	White et al, 1997[32]

HC/acetaminophen (7.5/750mg, q4-6h) Rofecoxib (50mg, qd) for 5 days	Acute pain, Functional endoscopic sinus surgery (FESS)	N=28 adult patients. 14/arm (from 40 enrolled)	R/DB	30% dropout rate Only assessed the mean peak pain score at each day for 4 days:	No differences in the common AEs: headache, drowsiness, constipation, sleep problem, nausea/vomiting	Church et al: 2006[15]
HC/acetaminophen (5/325mg) OX/acetaminophen (5/325mg)	Acute pain, Fracture with pain ≥5 on 0-10 scale	N=73 patients from ER; 34 HC/acetaminophen and 39 OX/acetaminophen	R/DB single-dose	No dropouts; Pain score at 30 and 60 min post dosing: OX/acetaminophen slightly better than HC/acetaminophen (but no stat significance)	Similar between 2 txs in common AEs: nausea, vomiting, itching, drowsiness; but HC/acetaminophen had higher % constipation.	Marco et al: 2005[33]
HC/acetaminophen (7.5/650mg) Tramadol/acetaminophen (75/650mg) placebo Single dose first 4 hr, then qid x5 days	Ankle sprain with partial ligament tear VAS≥50 mm (100-mm scale); NRS 2-3 (4-point)	N=204 HC/acetaminophen N=192 Tramadol/acetaminophen	R/DB/PC single- and multiple-dose	Dropout rate: 13% (due to AE and LOE); Analgesia at the first 4 hours: HC/acetaminophen & Tram/acetaminophen > placebo (P<0.05); no difference between HC/acetaminophen and Tram/acetaminophen For days 1-5: mean PR HC/acetaminophen=Tram/acetaminophen>Placebo, but no difference in mean PI and final PR/PI among 3 groups	Comparable between HC and Tram in common AEs: somnolence, nausea, vomiting, dizziness,	Hewitt et al: 2006[14]
HC/acetaminophen (10/650mg) Tramadol/acetaminophen (37.5/325mg) Tramadol/acetaminophen (75/650mg) placebo	Post-OP dental pain VAS≥50mm	N=200 patients; 50/arm	R/DB/PC/AC single-dose, 8-hr pain assessment	7.5% dropouts (with LOCF) Analgesia 0-8 hours post dosing: HC/acetaminophen & Tram/acetaminophen (75/650mg) > placebo (P<0.05) and HC slightly > Tram (but NS).	Common AEs: dizziness, nausea, vomiting, headache; HC>Tram	Fricke et al: 2002[34]

HC/acetaminophen (10/1000mg) Celecoxib 200mg Placebo Single-dose (8hr), Multiple dose (tid x5 days)	Orthopedic surgery Bunionectomy, ligament repair, open reduction and internal fixation of fracture, laminectomy or osteotomy VAS≥45mm	N=418 136-141/arm	R/DB/PC/AC single- and multiple-dose, placebo pts re-randomized to either tx for multiple-dose period	All treatments superior to placebo in PID during first 6-hour assessment; During the 5-day multiple dose, celecoxib superior to HC/acetaminophen	Overall common AEs: celecoxib was better than HC/acetaminophen	Gimbel et al: 2000[35]
HC/acetaminophen (10/1000 mg), Ketorolac (10 mg) placebo	Post-op dental pain	N=207 pts with moderate pain post dental procedure (65-68/arm)	R/DB/PC in acute pain, single dose, 6-hour pain assessment (PI on 4-point and 100-mmVAS, PR on 5-point)	Both active treatments were superior to placebo in SPID3 and SPID6, TOTPAR3 and TOTPAR 6; Ketorolac was superior to HC/acetaminophen combination	Higher frequency in HC/acetaminophen combination	Fricke at al 1993 [36]
HC/acetaminophen (7.5/500 mg), Codeine/acetaminophen (30/300 mg) placebo	Post-op dental pain	N=232 pts with moderate or severe pain post dental surgery	R/DB/PC single dose in acute pain, 6-hour pain assessment	Both treatments was superior to placebo, HC/acetaminophen was superior to codeine/acetaminophen	Typical opioid AEs	Forbes et al 1994 [37]

HC: hydrocodone (IR); acetaminophen: acetaminophen; OX: oxycodone (IR); IB: ibuprofen (IR); PC: placebo control; NS: not statistical significance

R: randomized, DB: double-blind, PC: placebo-controlled.

Appendix 2

Report from the Acute Liver Failure Study Group

Larson AM et al: Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study. ***Hepatology*** 42: 1364-1372, 2005[28]

Study Design: Historical prospective evaluation of demographic, clinical, laboratory and outcome information all subjects meeting entry criteria for acute liver failure (ALF) at the 22 academic centers participating in the ALF Study Group in US between Jan 1, 1998 and Dec 31, 2003 (6 calendar years).

ALF entry criteria:

- INR≥1.5
- Hepatic encephalopathy
- Within 26 weeks of illness onset without apparent chronic liver disease
- Informed consent from patients' legal next of kin (because of encephalopathy)
- Outcomes defined as liver transplantation, discharge or 3 weeks after admission

acetaminophen exposure information for each patient

- Total dose
- Type of acetaminophen product
- Duration of use

Criteria for causality between acetaminophen and ALF:

- A history of potentially toxic acetaminophen ingestion (*i.e.*> 4 g/day, the maximum dose recommended on the package) within 7 days of presentation;
- Detection of any level of acetaminophen in the serum; OR
- A serum ALT >1,000 IU/L with a history of acetaminophen ingestion, irrespective of the acetaminophen level
- Exclusion:
    - acute hepatitis A and B
    - hepatic ischemia
    - autoimmune hepatitis
    - Wilson disease

Confirmatory diagnosis:

- Case report forms reviewed by investigator at the central site (UTSW)
- Annual on-site audits conducted by the central site

ALF severity assessment:

- The Acute Physiology and Chronic Health Evaluation (APACHE) II score
- Model for End Stage Liver Disease (MELD) score
- The King's College Hospital criteria for ALF ("King's Criteria")

Definitions:

- Intentional (suicidal) ingestion: a single time-point ingestion in a patient admitting suicidal intent
- Unintentional ingestion: a multiple-time-point ingestion to relieve pain or other somatic symptoms with denial of suicidal intent.
- Alcohol abuse: was defined as consumption of ≥40 g alcohol per day in men and ≥20 g alcohol per day in women.

Results

Overall study population

- A total of 662 ALF cases (all causes) enrolled during the 6-year from the 22 centers, 302 cases (46% of 662) were acetaminophen-related hepatotoxicity with the following 17 exclusions:
  - 10 of them with insufficient data
  - 17 with competing causes: viral hepatitis, concomitant polydrug use or shock
- The 275 acetaminophen-related ALF cases (42% of 662) for final evaluation (Table 1),
  - acetaminophen-related ALF increased from 28% in 1998 to 51% in 2003 (Figure 1).
  - >80% of the patients were transferred from other institutions with significant encephalopathy (so compromising history taking)
  - The 22 participating centers represented approximately 30% of US transplant capability
  - An additional 40% of cases were not enrolled because of lack of informed consent or inadequate information to ensure the diagnosis
  - Estimated total acetaminophen-related ALF cases at US transplant centers: 250 per year

Type of acetaminophen products

- OTC products: 53% (n=147) used only OTC
  - 96% (n=141): single OTC product
  - 4% (n=6): two OTC products
- Rx products (opioid combo): 44% (n=120) used opioid/acetaminophen products
  - 28% (n=76): Rx only
  - 15% (n=41): Rx and OTC
- Concurrent use of 2 acetaminophen preparations: *22% overall*

Current antidepressant use

- 39% (n=108) ≥1 Rx antidepressant
- 12% (n=34): 2 or 3 simultaneously
- Females>males (46% vs. 20%)
- More likely to take opioid (17% vs. 5%) and opioid/acetaminophen (55% vs. 37%)

Unintentional vs. Intention overdose (Table 2)

- 44% (n=122): intentional

- 48% (n=131): unintentional
  - 79% for pain or constitutional symptoms
  - Many (n or %?) ingested modest amounts of acetaminophen over weeks or months
- 8% (n=22): unclear
- Differences between unintentional vs. intentional:
  - Older patients (median age: 38 yrs vs. 32 yrs)
  - *Multiple acetaminophen products (38% vs. 5%)*
  - Sought care longer after symptoms onset (media days: 4 vs. 1)
  - Less likely to report depression
  - Significantly lower serum acetaminophen level
  - Significantly lower ALT
  - More like to have severe hepatic encephalopathy
  - Similar history of past substance abuse
  - Similar education level
  - 19 patients with unintentional overdose used acetaminophen > 7 days

Opioid/acetaminophen use: (n=120, 44% of 275)

- 63% (n=83 of 131) unintentional, 18% (n=22 of 122) intentional
- 69% (n=83 of 120) were hydrocodone/acetaminophen (Vicodin)
- Clinical indictor of disease severity such as platelets, ALT, bilirubin: lower
- No difference in transplantation rate and overall survival
- *A third of narcotic users were simultaneously ingesting an OTC acetaminophen products (data not shown)*

History of substance abuse:

- Similar between unintentional group (35%) and intentional group (31%)
- Toxicology screens (all drugs of abuse including narcotics):
  - N=77 subjects (28% of 275) available
  - N=58 positive (75% of 77 or 21% of 275):
    - N=10: marijuana
    - N=11: cocaine
    - N=5: amphetamines
    - N=32: opiates, benzodiazepines, barbiturate or TCA or combinations
  - Not distinguished in illegal and legal narcotic use

Alcohol use and Abuse

- Chronic alcohol use: 55%
- Alcohol abuse: 35%
- Alcohol abusers vs. non-abusers
  - lower acetaminophen level
  - less likely to use antidepressants or narcotic combination
  - less likely to present with severe hepatic encephalopathy
- No differences between abusers and abstinent in INR, ALT, bilirubin, BMI, APACHE II score, MELD score or overall survival

- *65% patients with ≤ 4 acetaminophen/day were alcohol abusers and consumed greater alcohol than those taking > 4 g acetaminophen/day (data not shown)*

Acetaminophen dose:

- N=19 (7%) took acetaminophen ≤ 4 g/day
- Lower dose vs. higher dose:
  - Older
  - More unintentional
  - More often used or abused alcohol

Outcomes

- N=178 (65%) survived without liver transplantation: no significant differences from non-survivors in serum acetaminophen level, antidepressant use, total acetaminophen dose, type of overdose, narcotic or narcotic combination use, bilirubin, platelets, BMI, sex, age, ethnicity
- N=74 (27%) died
- N=23 (8%) underwent transplantation
- Overall, n=196 (71%) alive at the 3-week outcome point

Summary and Conclusion

1. acetaminophen-related hepatotoxicity accounted for at least 42% acute liver failure cases in US
2. Intentional and unintentional acetaminophen overdose almost equally contributed to the acetaminophen-related ALF.
3. 44% (n=120 of 275) were related to opioid/acetaminophen combination products, 69% (n=83 of 120) were hydrocodone/acetaminophen products and 30% (n=83 of 275) or 63% (n=83 of 131) were unintentional.
4. Overall 22% of patients simultaneously took 2 acetaminophen preparations.
5. A third of narcotic/acetaminophen users simultaneously took OTC acetaminophen products

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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
A089008	AA	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	CAPSULE; ORAL	500MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A081067	AA	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	CAPSULE; ORAL	500MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A040894	AA	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	SOLUTION; ORAL	325MG/15ML;7.5MG/15ML	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	BOCA PHARMA
A040418	AA	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	SOLUTION; ORAL	500MG/15ML;7.5MG/15ML	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MALLINCKRODT
A040881		Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	SOLUTION; ORAL	300MG/15ML;10MG/15ML	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A040482	AA	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	SOLUTION; ORAL	325MG/15ML;7.5MG/15ML	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A081051	AA	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	SOLUTION; ORAL	500MG/15ML;7.5MG/15ML	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART

A040366	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	SOLUTION; ORAL	500MG/15ML;7.5MG/15ML	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	NESHER PHARMS
A040834		Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	SOLUTION; ORAL	325MG/15ML;10MG/15ML	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	PHARM ASSOC
A040182	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	SOLUTION; ORAL	500MG/15ML;7.5MG/15ML	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	PHARM ASSOC
A040520	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	SOLUTION; ORAL	500MG/15ML;7.5MG/15ML	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VINTAGE PHARMS
A200343	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	SOLUTION; ORAL	325MG/15ML;7.5MG/15ML	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VISTAPHARM
A088058	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;5MG	VICODIN	ABBOTT
A040117	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	660MG;10MG	VICODIN HP	ABBOTT
A089736	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	750MG;7.5MG	VICODIN ES	ABBOTT
A040746	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	AMNEAL PHARMS NY
A040736	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	AMNEAL PHARMS NY
A040813	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	AMNEAL PHARMS NY

A040729	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	AMNEAL PHARMS NY
A040748	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	AMNEAL PHARMS NY
A040757	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	AMNEAL PHARMS NY
A040754	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	AMNEAL PHARMS NY
A040769	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	750MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	AMNEAL PHARMS NY
A201013	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	AUROLIFE PHARMA LLC
A201013	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	AUROLIFE PHARMA LLC
A201013	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	AUROLIFE PHARMA LLC
A090415	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	300MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	BOCA PHARMA
A090415	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	300MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	BOCA PHARMA
A090415	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	300MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	BOCA PHARMA

A040288		Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	400MG;10MG	ZYDONE	ENDO PHARMS
A040288		Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	400MG;5MG	ZYDONE	ENDO PHARMS
A040288		Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	400MG;7.5MG	ZYDONE	ENDO PHARMS
A040400	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MALLINCKRODT
A040409	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;5MG	ANEXSIA 5/325	MALLINCKRODT
A040405	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;7.5MG	ANEXSIA 7.5/325	MALLINCKRODT
A040201	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MALLINCKRODT
A089160	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;5MG	ANEXSIA	MALLINCKRODT
A040084	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MALLINCKRODT
A040201	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MALLINCKRODT
A040084	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MALLINCKRODT

A089725	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;7.5MG	ANEXSIA 7.5/650	MALLINCKRODT
A040084	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	660MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MALLINCKRODT
A040468	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	750MG;10MG	ANEXSIA	MALLINCKRODT
A040084	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	750MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MALLINCKRODT
A040556	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	300MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A040658	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	300MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A040556	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	300MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A040846		No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;2.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A040432	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A089698	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;2.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A089699	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART

A081223	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A040849		No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A089689	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	MIKART
A090118	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	SUN PHARM INDS INC
A090118	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	SUN PHARM INDS INC
A090118	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	SUN PHARM INDS INC
A090265	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	SUN PHARM INDS INC
A090265	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	SUN PHARM INDS INC
A090265	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	SUN PHARM INDS INC
A090380	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	SUN PHARM INDS INC
A090380	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	SUN PHARM INDS INC

A090380	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	660MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	SUN PHARM INDS INC
A090380	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	750MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	SUN PHARM INDS INC
A040100	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;10MG	LORTAB	UCB INC
A087722	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;5MG	LORTAB	UCB INC
A087757	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;5MG	CO-GESIC	UCB INC
A040355	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VINTAGE PHARMS
A040655	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VINTAGE PHARMS
A040656	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VINTAGE PHARMS
A040356	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VINTAGE PHARMS
A040144	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;2.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VINTAGE PHARMS
A089971	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VINTAGE PHARMS

A040144	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VINTAGE PHARMS
A040143	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VINTAGE PHARMS
A040155	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VINTAGE PHARMS
A040358	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	660MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VINTAGE PHARMS
A040157	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	750MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	VINTAGE PHARMS
A040148	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;10MG	NORCO	WATSON LABS
A040099	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;5MG	NORCO	WATSON LABS
A040148	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	325MG;7.5MG	NORCO	WATSON LABS
A040148	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	WATSON LABS
A081079	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;2.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	WATSON LABS
A089883	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	WATSON LABS

A081080	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	500MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	WATSON LABS
A040094	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	WATSON LABS
A040094	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	650MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	WATSON LABS
A040094	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	660MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	WATSON LABS
A040094	**AA**	Yes	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	750MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	WATSON LABS
A081083	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	750MG;7.5MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	WATSON LABS
A040495	**AA**	No	ACETAMINOPHEN; HYDROCODONE BITARTRATE	TABLET; ORAL	660MG;10MG	HYDROCODONE BITARTRATE AND ACETAMINOPHEN	WATSON LABS FLORIDA
N022439		Yes	CHLORPHENIRAMINE MALEATE; HYDROCODONE BITARTRATE; PSEUDOEPHEDRINE HYDROCHLORIDE	SOLUTION; ORAL	4MG/5ML;5MG/5ML;60MG/5ML	ZUTRIPRO	CYPRESS PHARM
A077273		No	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX	CAPSULE, EXTENDED RELEASE; ORAL	EQ 4MG MALEATE; EQ 5MG BITARTRATE	TUSSICAPS	HI-TECH PHARMA CO
A077273		Yes	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX	CAPSULE, EXTENDED RELEASE; ORAL	EQ 8MG MALEATE; EQ 10MG BITARTRATE	TUSSICAPS	HI-TECH PHARMA CO

A091632	**AB**	No	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX	SUSPENSION, EXTENDED RELEASE; ORAL	EQ 8MG MALEATE/5ML;EQ 10MG BITARTRATE/5ML	HYDROCODONE POLISTIREX AND CHLORPHENIRAMINE POLISTIREX	TRIS PHARMA INC
N019111	**AB**	Yes	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX	SUSPENSION, EXTENDED RELEASE; ORAL	EQ 8MG MALEATE/5ML;EQ 10MG BITARTRATE/5ML	TUSSIONEX PENNKINETIC	UCB INC
A088017	**AA**	No	HOMATROPINE METHYLBROMIDE; HYDROCODONE BITARTRATE	SYRUP; ORAL	1 5MG/5ML; 5MG/5ML	HYDROCODONE BITARTRATE AND HOMATROPINE METHYLBROMIDE	ACTAVIS MID ATLANTIC
A040613	**AA**	Yes	HOMATROPINE METHYLBROMIDE; HYDROCODONE BITARTRATE	SYRUP; ORAL	1 5MG/5ML; 5MG/5ML	HYDROCODONE BITARTRATE AND HOMATROPINE METHYLBROMIDE	HI TECH PHARMA
A088008	**AA**	No	HOMATROPINE METHYLBROMIDE; HYDROCODONE BITARTRATE	SYRUP; ORAL	1 5MG/5ML; 5MG/5ML	HYDROCODONE BITARTRATE AND HOMATROPINE METHYLBROMIDE	WOCKHARDT
A088508	**AB**	Yes	HOMATROPINE METHYLBROMIDE; HYDROCODONE BITARTRATE	TABLET; ORAL	1.5MG;5MG	TUSSIGON	KING PHARMS
A091528	**AB**	No	HOMATROPINE METHYLBROMIDE; HYDROCODONE BITARTRATE	TABLET; ORAL	1.5MG;5MG	HOMATROPINE METHYLBROMIDE AND HYDROCODONE BITARTRATE	NOVEL LABS INC
N020716	**AB**	Yes	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	7 5MG;200 MG	VICOPROFEN	ABBOTT
A076642		No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	10MG;200MG	REPREXAIN	AMNEAL PHARMS NY
A076642		No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	2 5MG;200 MG	REPREXAIN	AMNEAL PHARMS NY

A076 642	**AB**	No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	5MG;200M G	HYDROCODONE BITARTRATE AND IBUPROFEN	AMNEAL PHARMS NY
A076 642	**AB**	No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	7 5MG;200 MG	HYDROCODONE BITARTRATE AND IBUPROFEN	AMNEAL PHARMS NY
A076 023	**AB**	No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	7 5MG;200 MG	HYDROCODONE BITARTRATE AND IBUPROFEN	TEVA
A077 723	**AB**	No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	10MG;200M G	HYDROCODONE BITARTRATE AND IBUPROFEN	VINTAGE PHARMS
A077 727	**AB**	No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	5MG;200M G	HYDROCODONE BITARTRATE AND IBUPROFEN	VINTAGE PHARMS
A077 723	**AB**	No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	7 5MG;200 MG	HYDROCODONE BITARTRATE AND IBUPROFEN	VINTAGE PHARMS
A077 454	**AB**	No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	5MG;200M G	HYDROCODONE BITARTRATE AND IBUPROFEN	WATSON LABS FLORIDA
A076 604	**AB**	No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	7 5MG;200 MG	HYDROCODONE BITARTRATE AND IBUPROFEN	WATSON LABS FLORIDA
N022 442		Yes	HYDROCODONE BITARTRATE; PSEUDOEPHEDRI NE HYDROCHLORID E	SOLUTION ; ORAL	5MG/5ML;6 0MG/5ML	REZIRA	CYPRESS PHARM

BASIS FOR THE RECOMMENDATION TO MAINTAIN HYDROCODONE COMBINATION PRODUCTS IN SCHEDULE III OF THE CONTROLLED SUBSTANCES ACT

I. INTRODUCTION

The Food and Drug Administration (FDA) is recommending the continued control of hydrocodone combination products in Schedule III of the Controlled Substances Act (CSA). Hydrocodone substance was listed in Schedule II of the CSA upon the enactment of the CSA in 1971. At that time, hydrocodone combination products in specified doses (containing no greater than 15 milligram (mg) hydrocodone) were listed in Schedule III of the CSA when formulated with specified amounts of an isoquinoline alkaloid of opium or one or more therapeutically active nonnarcotic ingredients. Any other products that contain single entity hydrocodone or combinations of hydrocodone and other substances outside the range of specified doses are listed in Schedule II.

After receiving a Citizen Petition in 1999, requesting the rescheduling of hydrocodone combination products to Schedule II of the CSA, the Drug Enforcement Administration (DEA) in 2004 requested that the Department of Health and Human Services (HHS) provide a scientific and medical evaluation of the available information and a scheduling recommendation for hydrocodone combination products, pursuant to 21 U.S.C. 811(b) and (c).

Pursuant to 21 U.S.C. 811(b), the Secretary is required to consider in the scientific and medical evaluation eight factors determinative of control or removal of a drug or other substance from the schedules of the CSA. Pursuant to 21 U.S.C. 811(c), the Secretary shall consider the following factors with respect to each substance proposed to be controlled or removed from the schedules:

1. Its actual or relative potential for abuse.
2. Scientific evidence of the drug's pharmacological effects.
3. The state of current scientific knowledge regarding the drug or other substance.
4. Its history and current patterns 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 physiologic dependence liability.
8. Whether the substance is an immediate precursor of a substance already controlled.

Following consideration of the eight factors, the Secretary must make three findings to recommend scheduling a substance in the CSA. The three required findings relate to the substance's abuse potential, legitimate medical use, and safety or dependence potential.

U. S. Department of Justice
Drug Enforcement Administration

www.dea.gov

Washington, D.C. 20537

JUL 28 2004

Cristina V. Beato, M.D.
Acting Assistant Secretary for Health
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Beato:

The Drug Enforcement Administration (DEA) received a petition from [redacted] M.D., requesting the rescheduling of hydrocodone combination products from Schedule III to Schedule II of the Controlled Substances Act (CSA). As required by 21 U.S.C. §811(b) and (c), the DEA has gathered and reviewed the available data regarding the use, abuse and dependence of hydrocodone and products containing hydrocodone in response to this petition to determine whether hydrocodone products meet the criteria for Schedule II control. Our review of the enclosed data reflects that hydrocodone products are among the most widely abused, diverted and trafficked pharmaceutical drugs in the United States. Therefore, as required by 21 U.S.C. §811(b), we now request a scientific and medical evaluation and a scheduling recommendation from the Department of Health and Human Services (HHS) in order that this agency may reach its final determination on the petition to reschedule hydrocodone combination products. The DEA cannot complete its review of the petition until the HHS provides its scientific and medical evaluation of the available information and its scheduling recommendation.

The data which DEA has gathered in response to this petition is extensive, as hydrocodone has been utilized in medical practice as an antitussive agent and analgesic since the 1920s. When the CSA was enacted in 1971, hydrocodone was placed in Schedule II, while the products containing hydrocodone in specified amounts and in combination with other active ingredients were placed in Schedules III and V. Historically, hydrocodone was primarily utilized as a cough suppressant and was not widely prescribed. Today, hydrocodone products are increasingly utilized for pain management and are the most frequently dispensed opioid pharmaceuticals in the United States. In 2003, over 111 million prescriptions were dispensed for hydrocodone combination products.

Obviously, any attempt to restrict the use of hydrocodone products, which this requested reschedule would effectively cause, would be met with significant opposition. However, the benefit

Subject

of these products must be carefully considered together with chronic nationwide reports of their abuse and diversion. Despite their obvious utility in medical practice, as stated above, hydrocodone products are among the most popular pharmaceutical drugs associated with drug diversion, trafficking, abuse and addiction. The data gathered thus far shows that:

- Hydrocodone has an abuse liability similar to morphine. It is self-administered in animal models, will substitute for morphine in drug discrimination studies and produces effects that are substantially similar to morphine in both animals and humans. Hydrocodone is equipotent to morphine with respect to subjective effects, opiate signs and systems and "liking" scores.

- Hydrocodone products are associated with significant diversion. In every geographical area in the country, the DEA has listed this drug as one of the most commonly diverted drugs. Hydrocodone is the most frequently encountered opiate pharmaceutical in forensic laboratory submissions of drug evidence in federal, state and local facilities. Law enforcement has documented the diversion of millions of dosage units of hydrocodone by theft, doctor shopping, fraudulent prescriptions, bogus "call-in" prescriptions and diversion by registrants and Internet fraud.

- Hydrocodone products are associated with significant drug abuse. Hydrocodone was ranked 6th among all controlled substances in the 2002 Drug Abuse Warning Network (DAWN) emergency department data. In about 20 percent of all DEA diversion cases involving hydrocodone products, individuals claimed they were diverting hydrocodone products for their own personal use because they were addicted to hydrocodone. Increasing numbers of opiate abusers are entering treatment reporting hydrocodone as the primary, secondary or tertiary drug of abuse.

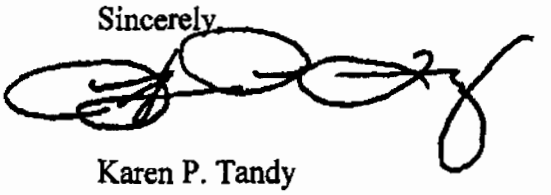
- Poison control data, DAWN medical examiner (ME) data and other ME data indicate that hydrocodone deaths are numerous, widespread and increasing in number. In addition, the hydrocodone acetaminophen combinations (accounting for about 80 percent of all hydrocodone prescriptions) carry significant public health risk when taken in excess.

- There is no data supporting a significant reduction in abuse potential or dependence profile of the hydrocodone combination products that could justify continued control in Schedule III of the CSA.

Appropriate members of the DEA staff are available to provide whatever assistance may be needed. In order to facilitate the exchange of information, the DEA staff is authorized to exchange

relevant information directly with designated members of your staff. Mr. William J. Walker, Deputy Assistant Administrator, Office of Diversion Control, will act as liaison for this exchange of information. He can be reached by telephone at (202) 307-7165.

Sincerely,



Karen P. Tandy
Administrator

Enclosure

Hydrocodone Combination Products:

An Eight-Factor Analysis

July 30, 2004

Prepared by:

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INTRODUCTION

Hydrocodone (substance) was placed in Schedule II of the Controlled Substances Act (CSA) when it was enacted in 1971. Hydrocodone combination products were placed in Schedule III and V depending on the concentration of hydrocodone. The Schedule III preparations include products with the following compositions:

(1) Not more than 300 mg of hydrocodone per 100 milliliter or not more than 15 mg of hydrocodone per dosage unit, with a fourfold or greater quantity of an isoquinoline alkaloid of opium, or

(2) Not more than 300 mg of hydrocodone per 100 milliliter or not more than 15 mg of hydrocodone per dosage unit, with one or more active nonnarcotic ingredients (e.g., acetaminophen, aspirin, or ibuprofen) in recognized therapeutic amounts.

It was generally believed that the addition of isoquinoline alkaloids or non-narcotic ingredients would reduce the abuse liability of these hydrocodone products. In addition, despite data that identified hydrocodone as a drug with significant analgesic efficacy, most hydrocodone products marketed in the U.S. at that time were intended for use as antitussive agents. Both the limited use of hydrocodone and the presumption of reduced abuse liability may have played a role in placing these products in Schedule III, although the Drug Enforcement Administration (DEA) could not identify any legislative history that specifically addressed the rationale for the original placement of these hydrocodone products in the CSA.

The DEA has received a petition from a practicing physician specializing in addiction medicine [redacted] The petition seeks to move Schedule III hydrocodone combination products to Schedule II of the CSA and cites the growing number of patients the petitioner personally treats who are addicted to these hydrocodone combination products and exhibit morphine-like dependence. The petitioner argues that these Schedule III products have a much higher abuse potential and more closely resemble Schedule II drugs.

Upon formal acceptance of the petition by the DEA, the Drug & Chemical Evaluation Section of the Office of Diversion Control has gathered the available data and completed a review of the eight factors required for any control changes requested in the petition in accordance with 21 U.S.C. § 811(c). The question being addressed in this review is whether the science and the experience gained by over 30 years of medical use, misuse, and abuse of Schedule III hydrocodone combination products support the continued lower placement of these medications in Schedule III.

FACTOR 1) ITS ACTUAL OR RELATIVE POTENTIAL FOR ABUSE:

A. ABUSE LIABILITY

All preclinical screening for abuse liability has involved the hydrocodone substance and NOT hydrocodone-combination products. Early clinical reports referring to the brand name "Dicodid" also involve a single entity hydrocodone formulation. References to the actual abuse or diversion of pharmaceutical products within the United States refer to hydrocodone-combination products as no single entity hydrocodone products are marketed in the U.S.

Preclinical Abuse Liability

Drug discrimination

The drug discrimination assay has been used to screen the abuse liability of drugs. Animal subjects are trained to emit one response under the direct effects of a drug and to make an identifiably different response while under the effects of a placebo. The only reliable stimulus which co-varies with food presentation is the subjective or interoceptive stimuli produced by the drug administration. Animals trained to discriminate the presence versus absence of morphine

tend to respond on the morphine-appropriate lever in a dose-dependent fashion. Drugs that produce morphine-like effects in these animal models show a significant concordance with drugs that show an opiate profile when tested in human opiate abuser populations. Therefore, the drug discrimination assay has a high predictive validity for the assessment of opiate-like effects in humans.

Rats that have been trained to discriminate the presence versus absence of 3 mg/kg of morphine sulfate engender a dose- and time-dependent cross-generalization to hydrocodone (Tomkins et al., 1997). The ED_{50} values for cross-generalization with the 3 mg/kg morphine training cue in these rats with 30 and 60 min pretreatment intervals were 0.5 and 0.7 mg/kg, respectively. Similar cross-generalization between morphine and hydrocodone was reported with rhesus monkeys (France *et al.*, 1996). These data suggest that hydrocodone produces subjective effects similar to morphine and predicts an equivalent abuse potential.

Chronic Drug Administration and Single-Dose Substitution:

In 1956, Deneau & Seevers reported to the Committee on Drug Dependence on their studies involving chronic drug administration in monkeys.. Seven drugs, in addition to morphine as the reference compound, were administered every 4 hrs for 30 days in different groups of monkeys (n=3). Hydromorphone (0.3 mg/kg) and hydrocodone (0.75 mg/kg) both produced "intermediate" intensities of abstinence signs after abrupt withdrawal on day 31 and nalorphine-induced abstinence produced morphine-like withdrawal signs on days 14 and 28. Deneau & Seevers (1956) concluded that these results were similar to those results obtained in man. In an earlier study (Deneau & Seevers, 1955), these authors chronically administered 3 mg/kg of morphine every 6 hrs to monkeys for 8 to 12 months. Morphine administration was abruptly discontinued. After 14 hours, substitution tests were conducted with various compounds to test whether they could suppress withdrawal signs. Hydrocodone (Dicodid, dihydrocodeinone) was found to be "very similar" to Dilaudid (hydromorphone) in its ability to suppress morphine abstinence signs. On a weight basis hydrocodone was found to be "slightly more potent than morphine".

In 1959, Deneau, McCarthy, & Seevers suggested that the rate and intensity of development of physical dependence (as measured by the intensity of abstinence and the capacities of various drugs, in comparison with morphine, to initiate physical dependence or suppress abstinence) are the only phenomena which are common to monkey and man which can be assessed objectively. Deneau, McCarthy & Seevers (1959) established a "monkey index" and "man index" and then, for comparison purposes, developed a correlation ratio between the two in an attempt to quantify the abuse liability of various opioid compounds. In their report to the Committee on Drug Dependence, Deneau, McCarthy & Seevers reported that 3 mg/kg of morphine in monkeys was equal to the suppressant capacity of 50 mg (total dose) in man. The correlation ratio between these two indices should be unity (equal to 1.0) if the quantitative capacities of the drugs are equal in both man and monkey in its ability to suppress abstinence. Hydrocodone was determined to be more potent than morphine in suppressing morphine abstinence in monkeys and equipotent to morphine in man.

Self-Administration

Self-administration of drugs by animals has been utilized as a preclinical predictor of abuse liability. Animals are frequently trained to work to receive a bolus of intravenous drug administration. The only "reward" these animals receive for pressing a lever is the delivery of a single bolus of drug injection. Drugs or drug doses which initiate and/or maintain lever-press responding above those levels engendered by saline administration are considered to produce a reward or motivation to continue to self-administer the drug. The self-administration task has been used to predict those drugs that would be classified as opiate-like or "addictive" in the human population (NIDA Research Monograph 52, 1984). Hydrocodone has been found to both initiate and maintain lever-press responding in rats at 0.16 mg/kg per injection dose (Tomkins *et al.*, 1997). The dose-related changes in the number of self-infusions administered in hourly test sessions were similar to those seen when morphine was self-administered in the rat. These data would predict a high abuse liability for hydrocodone in humans.

Summary

Hydrocodone is self-administered in animal models, will substitute for morphine in drug discrimination studies and was as effective as hydromorphone or morphine in suppressing morphine withdrawal. Taken collectively these data suggest that hydrocodone has an abuse liability similar to morphine.

Clinical Abuse Liability

The Advisory Committee on Traffic in Opium and Other Dangerous Drugs reported on hydrocodone (Dicodid) to the League of Nations in 1939. In their report they stated the following:

> It is well known and recognized that Dicodid (hydrocodone) creates euphoria and addiction.....There is no question but that Dicodid is able to create euphoria; it seems however that the euphoria is less intense than with morphine. R.F. Mayer states, on the other hand, that euphoria seemed to endure longer in his observations than that of morphine, because it does not have the same sleep-inducing effect as the latter (p 412).

Three separate clinical studies with hydrocodone were conducted by Fraser and Isbell and published in 1950. In *Experiment #1*, single doses of four test drugs (morphine, morphinan, 6-methyldihydromorphine, and hydrocodone) were administered to 10 or more former morphine addicts. These subjects reported that 20 mg of hydrocodone produced a grade of euphoria equivalent to that induced by 30 mg of morphine. When administered intravenously the euphoric effects were more intense when compared to the subcutaneous route of administration. In *Experiment #2*, tests were conducted on two human subjects that were maintained on 480 mg of morphine a day. Thirty hours after their last dose of morphine, at a time when both subjects were experiencing signs of "severe withdrawal," subjects received a dose of 45 mg of hydrocodone. Hydrocodone substitution produced a sharp decline in the intensity of the opiate withdrawal syndrome for 6 to 8 hours after its administration. *Experiment #3* was conducted in five "healthy" adult male volunteers with a history of morphine addiction. Each subject was abstinent for at least six months prior to the study. Administration of subcutaneous escalating and divided

doses of hydrocodone were conducted over 38 days. The terminal dose, achieved on day 17 of the study, was 240 mg (60 mg q.i.d.). No significant changes in rectal temperature, pulse rate, or systolic blood pressure were noted at any time. Miosis was observed throughout the study. All subjects liked the effects of hydrocodone and compared them favorably with morphine (Fraser & Isbell, 1950). Definite tolerance to the sedative action of the drug was seen but complete tolerance did not develop before the experiment terminated (Isbell, 1949). There was a general slowing of the EEG waveforms that progressed as the dose of hydrocodone was raised. This pattern was reported to be similar to those EEG changes occurring during chronic morphine administration. The abstinence or withdrawal syndrome that developed after the last dose of the 38-day hydrocodone treatment was similar to, but milder than, the syndrome produced from chronic morphine administration. The intensity of the abstinence syndrome varied greatly in the different individuals (Isbell, 1949). However, in comparison, the hydrocodone-withdrawal syndrome was greater than that reported after chronic codeine administration but followed a similar time-course. Fraser & Isbell, in their 1950 published report, re-voiced the conclusions of the Committee on Drug Addiction and Narcotics and stated the following:

> The total addiction liability of dihydrocodeinone [hydrocodone, *sic*] must therefore be regarded as being more nearly comparable to the addiction liability of morphine than it is to the addiction liability of codeine (Fraser & Isbell, 1950, p. 134).

In 1967, Jasinski & Martin assessed the dependence-producing properties of hydrocodone in male volunteers at the U.S. Public Health Service Hospital in Lexington, Kentucky. Hydrocodone and codoxime were compared with morphine sulfate in 10 subjects, using a double-blind cross-over design. The subjective effects were assessed for 12 hours following intramuscular administration of the three drugs. Time-effect functions were assessed for the first four hours after single drug test sessions for mean pupillary constriction, opiate signs, opiate symptoms, "liking" scores (assessed by the research technicians), and "liking" scores (assessed by the subjects). All measures from these acute dose tests indicated that hydrocodone and

morphine were equipotent and produced equivalent drug-effects. There were no marked differences among the time-effect functions of the three drugs tested and all effects showed dose-response functions, as well. To further examine the opiate-like nature of hydrocodone, the drug was tested for its ability to suppress the signs and symptoms of opiate abstinence syndrome in 7 additional subjects chronically administered 240 mg of morphine sulfate per day. Abstinence was assessed from the 14th through the 24th hr after the last dose of morphine was administered using an 11-point scale. Hydrocodone was able to substitute for morphine and diminish the intensity of the abstinence syndrome, evidence defined by the authors as a measure of the physical dependence producing properties of hydrocodone.

Baumann et al. (1993) compared methadone and hydrocodone substitution treatment for heroin addiction. Hydrocodone was found to substitute for heroin and was determined to be as effective (as measured by employment, prostitution and criminality) as methadone in maintenance treatment for opioid addiction.

Zacny (2003) characterized the subjective, psychomotor, and physiological effects of a hydrocodone combination product (Hycodan) in non drug-abusing volunteers. Eighteen volunteers participated in a crossover double-blind study in which they received orally administered placebo, 5 mg hydrocodone/1.5 mg homatropine, 10 mg hydrocodone/3 mg homatropine, 20 mg hydrocodone/ 6 mg homatropine, 40 mg morphine and 2 mg lorazepam. Measures were assessed before and for 300 minutes after drug administration. End-of-session and 24-hour measures were taken to assess residual drug effects and overall subjects' assessment of the drug effects. Subjective effects for all hydrocodone combinations were dose-related; 20 mg of Hycodan produced subjective effects equivalent to 40 mg of morphine. Cognitive and psychomotor impairment were more marked with lorazepam. Post-session ratings of overall liking and "want to take drug again" were not significant for morphine or hydrocodone/homatropine at oral doses tested in this paradigm. This data is consistent with a number of studies which have noted minimal-to mild impairment with clinically prescribed doses of mu agonist opioids (cf. Zacny, 1995).

Summary

In summary, the abuse liability of hydrocodone has been examined and reviewed by a number of researchers. The data indicate that:

- Hydrocodone can substitute for morphine or heroin in opiate-dependent subjects and produces effects substantially similar to morphine in both animals and humans.
- Hydrocodone is equipotent to morphine with respect to subjective effects, opiate signs, opiate symptoms and "liking" scores.
- Hydrocodone is more potent than morphine in suppressing morphine abstinence syndrome in monkeys but is equipotent in suppressing the syndrome in man. In comparison, Dilaudid (hydromorphone hydrochloride) was found to be less potent than morphine in both monkey and man.
- Drug discrimination and self-administration studies conducted in both rats and monkeys demonstrate similar abuse and dependence liabilities for both hydrocodone and morphine.

These data suggest that the original placement of hydrocodone in Schedule II of the CSA was an appropriate placement based on abuse potential, medical use and dependence profile. The DEA could not identify any studies that might have provided a scientific basis for placing hydrocodone combination products in lower schedules. Hydrocodone combination products have not been compared to hydrocodone alone in any of the paradigms utilized to examine abuse liability. Only one study was identified that compared the effects of acute dosing of a hydrocodone combination product (Hycodan; hydrocodone and homatropine combination) to morphine. Twenty mg of Hycodan (PO) produced effects substantially similar to 40 mg morphine (PO).

B. ACTUAL ABUSE

With the exception of illegal Internet purchases of hydrocodone products, the diversion, trafficking and abuse of hydrocodone are almost entirely associated with pharmaceutical products manufactured, distributed and prescribed within the U.S. There is no clandestine production of this substance. Collectively, hydrocodone combination products are the most prescribed pharmaceutical opiates in the U.S. The production and prescription of these products have increased dramatically in recent years. At the same time, all data sources indicate that hydrocodone products are extensively diverted and abused. In some instances, the abuse of hydrocodone products has been associated with considerable morbidity/mortality.

Production and Distribution: DEA DATA

As a Schedule II substance, the DEA establishes a yearly aggregate production quota (APQ) for hydrocodone. Table 1 lists the APQ for hydrocodone for the years 1990 through 2003.

TABLE 1. Hydrocodone Aggregate Production Quota 1990-2003

YEAR	APQ KG ANHYDROUS HYDROCODONE	YEAR	APQ KG ANHYDROUS HYDROCODONE
1990	4,473	**1997**	13,891
1991	4,582	**1998**	16,314
1992	5,757	**1999**	20,208
1993	7,404	**2000**	21,417
1994	8,344	**2001**	23,825
1995	8,474	**2002**	23,825
1996	12,145	**2003**	25,702

These values reflect the amount of hydrocodone that can be legitimately manufactured in the U.S. and include amounts needed for patient care, research and product development, export and inventory, but exclude amounts of hydrocodone manufactured for conversion to other drugs. The amount of hydrocodone manufactured for medical use in the U.S. has increased by more than 400 % since 1990.

[redacted] In March 2004, there were 116 active dosage form manufacturers registered with the DEA. Many companies are manufacturing newer products with higher total dose amounts per tablet. This likely reflects the increased use of hydrocodone for analgesia rather than cough suppression.

The DEA ARCOS (Automation of Reports and Consolidated Order System) database tracks the purchases of all Schedule II substances and Schedule III narcotics from distributors to pharmacies, hospitals, clinics, doctors and teaching institutions. The system does not capture patient-specific statistics nor provide direct information about prescribers.

ARCOS is generally used as a law enforcement tool; unusual sales or purchases may trigger a DEA investigation. However, ARCOS data also gives a fair approximation about the general use of these controlled substances in various states and communities. The ARCOS yearly cumulative consumption of hydrocodone for 1990 through 2002 for the United States and its protectorates is summarized in Table 2. Nationally, the amount of hydrocodone sold for ultimate consumer use rose by over 600 % during this time period. Table 3 provides a list of the top ten hydrocodone consumer states in 2002. Nevada, the top consumer of hydrocodone, used three times the national average.

TABLE 2.

YEAR	CUMMULATIVE CONSUMPTION GRAMS PER 100,000 U.S. POPULATION
1990	845
1991	982
1992	1,084
1993	1,238
1994	1,404
1995	1,604
1996	1,858
1997	3,189
1998	3,838
1999	4,357
2000	5,357
2001	5,615
2002	6,635

TABLE 3.

STATE Ranking 2002		*GRAMS/100,000 POPULATION*
1	NEVADA	20,363
2	KENTUCKY	13,605
3	ALABAMA	12,568
4	WEST VIRGINIA	12,021
5	LOUISIANA	11,743
6	TENNESSEE	11,615
7	OKLAHOMA	11,091
8	TEXAS	9,494
9	ARKANSAS	9,154
10	INDIANA	8,939

Prescription data

The estimated numbers of new, renewed and total hydrocodone prescriptions derived from pharmacy audits conducted by IMS Health for the years 1994 through 2003 are listed in

Table 4. For comparative purposes, prescriptions for codeine and oxycodone combination products are also provided. Over the last several years codeine prescriptions have been declining while hydrocodone prescriptions have been escalating. Oxycodone combination products have increased far less than oxycodone single entity products and the total number of prescriptions for hydrocodone products is about five-times greater than for oxycodone combination products.

TABLE 4. IMS Health estimates of new, renewed, and total prescriptions for codeine (COD), hydrocodone (HYD) and oxycodone (OXY) combination products

YEAR	New Rx (x 1000)			Renewed Rx (x 1000)			Total Rx (x 1000)		
	COD	OXY	HYD	COD	OXY	HYD	COD	OXY	HYD
1994	22,829	10,242	30,093	5,295	38*	7,769	28,127	10,281	37,764
1995	38,184	12,036	44,031	8,188	129*	10,612	46,372	12,165	54,643
1996	35,519	12,661	46,293	7,568	93*	11,431	43,085	12,754	58,724
1997	33,482	13,827	51,114	7,146	151*	12,487	40,628	13,978	63,600
1998	32,427	13,624	57,099	6,795	134*	13,921	39,222	13,759	71,020
1999	33,868	14,665	65,736	6,850	208*	15,988	40,718	14,873	81,724
2000	30,970	15,872	71,447	6,300	132*	17,329	37,366	16,003	88,776
2001	30,251	17,251	76,910	6,111	183*	19,404	36,461	17,434	96,315
2002	28,797	19,473	82,741	5,850	333*	20,900	34,647	19,706	103,641
2003	28,479	21,459	88,267	5,469	287*	22,747	33,948	21,746	111,014

*** Oxycodone is a Schedule II substance which limits its availability as a renewed prescription. IMS records a low number of renewed prescriptions from long-term care facilities and hospice care facilities and reflects partial filling and refilling of the original prescriptions.**

Of these three commonly prescribed combination products, hydrocodone clearly leads the triad in the prescribing practices of health care professionals with over 111 million prescriptions dispensed in 2003 alone. Of these prescriptions, about 80% were for solid dosage forms (i.e. pills) and of those prescriptions, over 90% were for hydrocodone in combination with acetaminophen. This combination is associated with certain health risks when very high doses are consumed (see Factor 6).

Diversion & Abuse of Hydrocodone-combination Products

In 1992 and 1993, the United States report to the U.N. Drug Control Program (Annual Reports Questionnaire) documented a stable diversion of hydrocodone of approximately 200,000 dosage units per year. In 1994 the United States documented the diversion of hydrocodone at over 7 million dosage units for the year, and in 1997 the diversion rose to well over 11 million dosage units. From January 1, 2001 through December 31, 2003 there were over 17 million dosage units of hydrocodone products reported to DEA as drug theft/loss by registrants. The increase in the diversion of licit hydrocodone suggests a pattern of misuse and abuse in the general population.

Forensic Laboratory Data

The figures (below) represent the total number of cases and exhibits associated with state and local law enforcement activities involving hydrocodone, codeine, and oxycodone that were analyzed in laboratories affiliated with the National Forensic Laboratory Information System (NFLIS). NFLIS is a DEA-contracted laboratory data collection system of state and local forensic laboratories throughout the United States. NFLIS cannot be used for 'trending' analyses since new labs were added each year. Hydrocodone is among the top 10 most frequently encountered drugs in the NFLIS system and is the leading diverted controlled pharmaceutical opiate.

FIGURE 1. **NFLIS DATA**

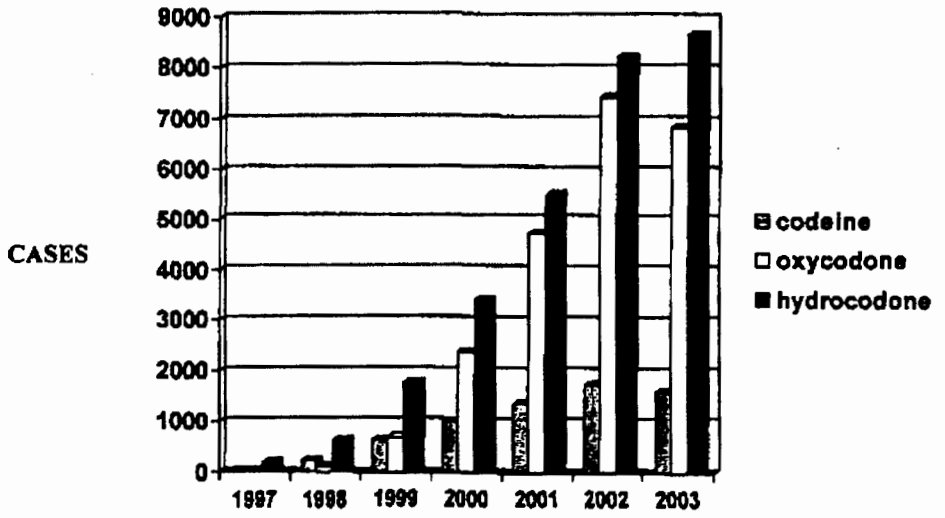
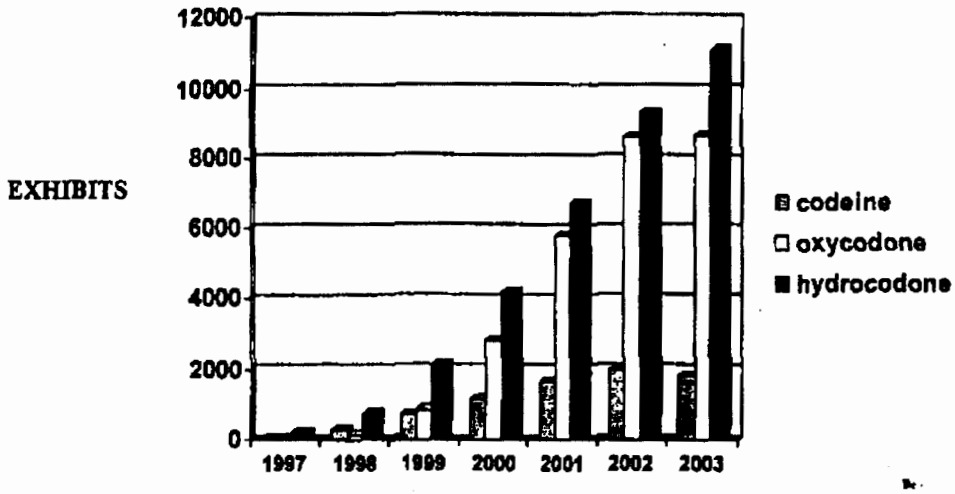


FIGURE 2. **NFLIS DATA**



Codeine was selected as a comparator because it is similarly scheduled with the same indications for medical use as hydrocodone. Oxycodone, a Schedule II substance, was selected for comparison because these products have been associated with considerable diversion and abuse in recent years.

STRIDE Data

Table 6A, 6B, and 6C present the total number and type of hydrocodone (6A), codeine (6B), and oxycodone (6C) exhibits entered into the DEA STRIDE (System to Retrieve Information on Drug Evidence) for 1994 through 2003. The STRIDE data contain those drug exhibits analyzed in the DEA forensic laboratory system that have been submitted to the laboratory as drug evidence from seizures and undercover purchases. State and local cases involving drug evidence represent a majority of the cases involving pharmaceutical products and are not captured in the STRIDE system. Generally, the STRIDE database does not list the actual or suspected dosage strengths. As a consequence, no differentiation can be made as to the actual dose of each tablet, capsule or liquid that was seized and analyzed. Neither STRIDE nor NFLIS data reflect the actual magnitude of the diversion of any pharmaceutical drug. For example, cases involving forged prescriptions, bogus call-in prescriptions, drug theft, doctor shopping or diversion of medications by registrants (for example, physicians and pharmacists) for personal use/abuse, rarely have drug evidence to be analyzed. Despite these deficiencies, forensic

laboratory data does document the illicit availability (diversion and trafficking) of a pharmaceutical substance.

The total number of federal cases and exhibits of hydrocodone associated with evidence submitted to STRIDE for the years 1996 through 2003 are seen in Table 5.

TABLE 5. STRIDE CASES AND EXHIBITS

	Cases	Exhibits
1996	54	136
1997	54	184
1998	56	89
1999	96	232
2000	104	255
2001	117	272
2002	145	298
2003	171	468

TABLE 6A. STRIDE HYDROCODONE UNITS

YEAR	TABLETS	CAPSULES	POWDER (GRAMS)	LIQUID (MLS)
1994	10,326	63	1	2,615
1995	13,253	705	31	8,466
1996	58,191	2,345	901	1,018
1997	132,350	143	136	15,786
1998	67,386	-	265	219
1999	21,029	14	1,268	456
2000	69,133	55	428	5,252
2001	12,573	38	459	7,504
2002	33,502	164	2,592	7,036
2003	61,483	534	179	11,958
Total	**479,226**	**4,061**	**6,260**	**60,310**

TABLE 6B. STRIDE CODEINE UNITS

YEAR	TABLETS	CAPSULES	POWDER (GRAMS)	LIQUID (ML)
1994	5,492	62	1	1,095
1995	3,669	377	30	119
1996	50,692	2,333	901	415
1997	2,217	551	3,560	1,114
1998	5,991	96	129	6,122
1999	8,108	521	687	11,400
2000	27,843	672	21,743	42,652
2001	1,689	43	2	16,197
2002	2,496	1,111	46	44,069
2003	16,331	2,149	959	152,596
TOTAL	**124,528**	**7,915**	**28,058**	**275,779**

TABLE 6C. STRIDE OXYCODONE UNITS

YEAR	TABLETS	CAPSULES	POWDER (GRAMS)	LIQUID (ML)
1994	8,823	386		
1995	2,478	1		
1996	4,644	56	138	
1997	4,244	120	93	
1998	27,685	76		
1999	5,651	345		
2000	43,449	184	214	31
2001	81,450	339	2,185	92
2002	19,598	1,438	34	393
2003	53,248	1,052	670	348
TOTAL	**251,070**	**3,997**	**3,334**	**864**

In summary, forensic laboratory data, NFLIS and STRIDE, have documented the diversion and trafficking of hydrocodone, codeine and oxycodone products. Comparatively, hydrocodone exhibits are the most frequently encountered of all opioid pharmaceuticals and tablets are the most common form of this substance. It is important to note that these numbers do not reflect the total amount of diverted drug for any year. Data gathered for total diverted drug include STRIDE, drug theft reports, other Federal agency seizures and any available state and local data (including NFLIS). For example, hydrocodone drug theft/loss data for 2003 totaled over 7.4 million dosage units.

Poison Control Data

The Toxic Exposure Surveillance System (TESS) data are compiled by the American Association of Poison Control Centers (AAPCC) in cooperation with the majority of the United States poison centers. The data collection system was designed to identify hazards so that education, research and training might be initiated in advance of a serious threat to the health of the general population. TESS data cannot be trended because of variability in reporting units and populations served.

In 2002, there were 2,380,028 human exposure cases reported by 64 participating poison centers (63 submitted data for the entire year) and a total population of 291.6 million people were served including 49 entire states (all except North Dakota). Table 7 represents 2002 data for selected narcotic analgesics including total number of exposures, breakdown for age and reason for exposure (unintentional or intentional). INT exposures include suspected intentional suicide and intentional drug misuse/abuse. Table 8 provides additional 2002 TESS data regarding the severity of the exposures associated with the same opioids listed in Table 7. The following definitions apply to severity of exposures:

> Minor Effect: The patient developed some signs or symptoms as a result of the exposure but they were minimally bothersome and generally resolved rapidly with no residual disability or disfigurement
> Moderate Effect: The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged or more systemic in nature than minor symptoms. Usually, some form of treatment is necessary. Symptoms are not life-threatening and the patient had no residual disability or disfigurement.
> Major effect: The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement.

Death: The patient died as a result of the exposure or as a direct complication of the exposure. Only those deaths that were probably or undoubtedly related to the exposure are coded.

TABLE 7. TESS 2002- Opioid analgesic exposures

ANALGESIC	NUMBER OF EXPOSURES	AGE			REASON	
		<6	6-19	>19	UNINT	INT
Codeine	7,438	1,560	1,546	4,283	3,245	3,545
Hydrocodone	17,429	1,585	2,648	12,959	5,672	10,282
Meperidine	558	42	59	447	198	250
Methadone	2,747	156	260	2,300	712	1,697
Morphine	2,327	208	269	1,815	967	1,064
Oxycodone	10,515	1,019	1,324	8,037	3,992	5,450
Pentazocine	187	10	18	158	72	78
Propoxyphene	6,576	732	837	4,956	2,299	3,885
Tramadol	2,400	286	293	1,794	826	1,316

TABLE 8. TESS 2002- Opioid analgesic exposures and outcome measures

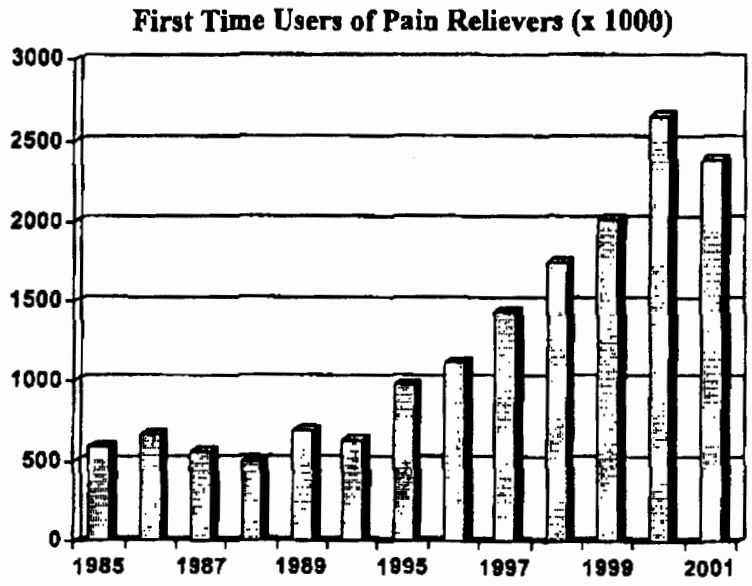
ANALGESIC	TREATED IN HEALTH CARE FACILITY	OUTCOME			
		MINOR	MODERATE	MAJOR	DEATH
Codeine	3,995	1,667	699	30	20
Hydrocodone	10,562	4,326	2,039	531	66
Meperidine	337	129	96	21	4
Methadone	1,956	493	649	345	89
Morphine	1,361	437	366	147	37
Oxycodone	5,941	2,373	1,397	457	63
Pentazocine	99	51	20	4	2
Propoxyphene	4,219	1,636	828	243	43
Tramadol	1,585	590	387	103	8

In 2000, Hoppe-Roberts, Lloyd & Chyka compared the TESS system statistics to the National Center for Health Statistics (NCHS) data and concluded that poisoning deaths reported in the U.S. poison control centers represent only 5 per cent of the number of deaths tabulated by national death certificates. That conclusion may limit the generalizability of the TESS data as they relate to the total number of hydrocodone related deaths in the U.S. However, in comparing hydrocodone TESS data to other opioid analgesics TESS data for 2002, hydrocodone is 2nd only to methadone in drug-related deaths and is associated with significantly greater health care burden than any other opioid pharmaceutical.

Drug Abuse Survey Data:

The National Household Survey on Drug Abuse (NHSDA) is conducted each year by the Substance Abuse Mental Health Services Administration. Data from this survey clearly demonstrate the growth in the abuse of pain relievers over the last two decades. The estimated number of respondents reporting first time use of a prescription pain reliever has been rising since 1989. The term "first time use" is defined as taking a pain reliever that was not prescribed for the respondent and that they reportedly took only for the experience or feeling the drug caused. Figure 3 shows the rising first time use of pain relievers for all age groups (source: National Household Survey on Drug Abuse 2002, SAMHSA, Table H.39).

Figure 3.



The estimated total number of non-medical users of pain relievers has also shown significant increases over the last few years of the survey (prior surveys reported these data as percentages of total samples). According to the 2002 National Survey on Drug Use and Health, there were over 10.9 million Americans using prescription pain relievers non-medically with over 4.3 million current abusers (see Table 9 below).

TABLE 9 Non-medical use of pain relievers in 2002

Year	Lifetime Users	Past Year Users	Last Month Users
2000	19,210,000	6,466,000	3,849,000
2001	22,133,000	8,353,000	4,811,000
2002	29,611,000	10,992,000	4,377,000

These data indicate that an ever increasing number of individuals are abusing opioid analgesics. Individuals who chose to traffic in these drugs have a ready market for their products and can amass a considerable profit from their activity. Pharmaceutical opiates (including hydrocodone products) have substantial value on the illicit market. Because hydrocodone products are currently in Schedule III of the CSA, the regulatory controls placed on these drugs is less restrictive than Schedule II controls. For example, prescription refills and call-in prescriptions are permitted. Law enforcement data indicate that tampered/fraudulent prescriptions and bogus call-in prescriptions are major sources of diverted hydrocodone products.

DAWN Emergency Department Data

The Drug Abuse Warning Network (DAWN) reports national estimates of emergency department episodes and mentions involving hydrocodone within the United States. The objectives of the DAWN system are to identify drugs and other substances currently being abused and to provide demographic and other data pertaining to drug abuse for national and local drug abuse policy and planning. Drug abuse for DAWN has been defined as the nonmedical use of a

drug or substance for psychic effect, for suicide attempt or gesture, or for reasons of dependence. The definition of non-medical use means the use of prescription drugs in a manner inconsistent with accepted medical practice and the use of over-the-counter drugs contrary to the approved labeling. Emergency Department episodes involving the nonmedical use of legal drugs involve the deliberate misuse/abuse of prescribed or legally obtained medications or of pharmaceuticals diverted for abuse. Accidental overdoses or ingestions with no intent of abuse, or adverse reactions to prescription drugs taken as directed are NOT reportable to DAWN unless they were present in combination with an illicit drug.

The DAWN data reflect drug use which is self-reported by emergency room patients and may under-represent incidence of prescription drug abuse. It may also under-represent drug abuse episodes associated with major trauma, because these patients are often not in a position to give a history of drug abuse while being treated in the emergency departments. Medical records generated after the patient has left the emergency room, which may include important toxicology reports, are generally not available to the individual hospital employee who serves as the DAWN reporter (Gruberg, Wright & Gfroerer, 1998). These factors highlight some important "error" variables in the DAWN data when it comes to over-the-counter medications or prescription drugs.

The published DAWN data for the period spanning 1976 through 1985 were reviewed, analyzed for trends, and rank ordered by the Division of Epidemiology and Statistical Analysis of the National Institute on Drug Abuse in 1987. Hydrocodone was not even listed as one of the top 80 ranked drugs for any year of the decade analyzed in the review. During that time, the primary use of hydrocodone in the U.S. was for cough suppression. In recent years, however, hydrocodone has consistently ranked among the top 20 controlled substances in DAWN and in 2002, hydrocodone ranked 6th among all controlled substances.

In 2002, 3.8 % of all DAWN ED episodes were for hydrocodone. Table 10 lists the cities that ranked highest for hydrocodone abuse (as determined by averaging percent of total episodes for hydrocodone for 1992 through 2001). The ranking and percent of total episodes for 2002 is also listed. A number of cities reporting to DAWN have fairly high rates of ED episodes for hydrocodone.

TABLE 10 Areas ranking highest in DAWN ED episodes for hydrocodone (1992-2001)

1992-2001			2002		
Rank		**(% Total Episodes)**	**Rank**		**(% of total episodes)**
1.	SAN DIEGO	(4.3)	*1.*	New Orleans	(6.1)
2.	DALLAS	(3.5)	*2.*	Dallas	(6.0)
3.	PHOENIX	(2.6)	*3.*	Buffalo	(4.2)
4.	LOS ANGELES	(2.5)	*4.*	San Diego	(4.0)
5.	SAN FRANCISCO	(2.1)	*5.*	Minneapolis-SP	(3.7)
6.	MINNEAPOLIS-SP	(2.1)	*6.*	Phoenix	(3.2)
7.	SEATTLE	(2.0)	*7.*	Detroit	(3.1)
8.	DENVER	(1.7)	*8.*	Denver	(2.9)
9.	NEW ORLEANS	(1.6)	*9.*	San Francisco	(2.5)
10.	ATLANTA	(1.3)	*10.*	St Louis	(2.5)

Table 11 lists the estimated number of emergency department (ED) episodes involving hydrocodone, codeine and oxycodone for 1994 through 2002.

TABLE 11. DAWN: Number of ED Mentions of Codeine, Hydrocodone and Oxycodone

YEAR	CODEINE	HYDROCODONE	OXYCODONE
1994	9,439	9,320	4,069
1995	8,732	9,686	3,393
1996	7,594	11,419	3,190
1997	7,869	11,570	5,012
1998	6,620	13,611	5,211
1999	4,974	15,252	6,429
2000	5,295	20,098	10,825
2001	3,720	21,567	18,409
2002	4,961	25,197	22,397
% Change 1994-2002	-47%	170%	450%

In the revised estimates of ED episodes released in Spring 2002, DAWN reported significant long-term increases for hydrocodone, up 131 % from 1994 to 2000. From 1998 to 2000, ED mentions increased 48 % for hydrocodone, with a 32 % increase reported between 1999 and 2000 and another 7.3 % increase between 2000 and 2001. From 1992 through 2001, 2 % of all DAWN episodes were for hydrocodone.

In recent years, the number of ED episodes related to hydrocodone combination products (CIII) far exceeds that of codeine combination products (primarily CIII). While codeine episodes are declining, hydrocodone episodes continue to escalate. One might argue that this simply reflects the much greater availability of hydrocodone products due to much greater prescription of hydrocodone compared to codeine. However, if you normalize DAWN episodes by dividing them by the number of prescriptions, the rate of hydrocodone episodes per prescription is more than twice that of codeine for 2002. ED episodes resulting from oxycodone use were relatively stable until the recent introduction of the sustained release single entity product - OxyContin®. While the ED estimates are still greater for hydrocodone, oxycodone episodes are rapidly increasing and the rate of DAWN episodes per prescription is greater for oxycodone.

To clarify the nature of the abuse patterns, the demographic analysis of the DAWN hydrocodone data for the years 1994 through 2001 are broken down by age, sex, and race, in Tables 12 through 14, respectively. Using this data and other information provided by the patient (including source of the drug, other drugs taken in combination with hydrocodone, purported reason for taking the drug), a profile of a typical hydrocodone abuser emerges. According to DAWN, the hydrocodone abuser is likely to be a white female, older than 25 years of age, who is taking hydrocodone tablets orally in combination with alcohol for dependence or suicide. Most patients report obtaining hydrocodone from prescriptions although no information is provided about the legality of those prescriptions (i.e., were they forged, purchased from illegal internet pharmacies, altered, obtained by doctor shopping or bogus call-ins). Nearly 10 % do report obtaining hydrocodone through illicit purchases.

TABLE 12. Estimated number and percent distribution of hydrocodone mentions by age group over the period of 1994 through 2001

YEAR		AGES					
		12-17	18-25	26-34	35+		Total
1994	estimate	921	1,764	2,962	3,493		9,320
	% of total	9.9	18.9	31.8	37.5		
1995	estimate	487	1,954	3,029	4,212		9,686
	% of total	5.0	20.2	31.3	43.5		
1996	estimate	957	1,820	3,504	5,135		11,419
	% of total	8.3	15.9	30.7	45.0		
1997	estimate	686	2,615	2,914	5,353		11,570
	% of total	5.9	22.6	25.2	46.3		
1998	estimate	1,337	2,482	2,718	7,018		13,611
	% of total	9.8	18.2	20.0	51.6		
1999	estimate	693	2,294	3,376	8,839		15,252
	% of total	4.5	15.0	22.1	57.8		
2000	estimate	1,081	2,860	4,747	11,360		20,098
	% of total	5.4	14.2	23.6	55.5		
2001	estimate	708	3,606	5,555	11,682		21,567
	% of total	3.3	16.7	25.7	54.1		

Since 1994, the average age of an individual coming into the emergency room for hydrocodone abuse is increasing. In 2001, 54.1 % of all hydrocodone ED visits were associated with individuals 35 years of age or older.

TABLE 13. Estimated number and percent distribution of hydrocodone mentions by sex over the period of 1994 through 2001

Year	Males		Females		Unknown	
	estimate	% of total	estimate	% of total	estimate	% of total
1994	3,703	39.7	5,420	58.1		0.0
1995	3,679	38.0	5,981	62.0	26	0.0
1996	4,516	39.5	6,754	59.1		0.0
1997	4,547	39.5	6,881	59.5		0.0
1998	5,044	37.0	8,420	61.9		0.0
1999	6,414	42.0	8,643	56.8		0.0
2000	8,226	40.9	11,653	58.0		0.0
2001	7,767	36.0	13,461	62.4	339	1.6

TABLE 14. Estimated number and percent distribution of hydrocodone mentions by ethnicity over the period of 1994 through 2001

	White		Black		Hispanic		Race/Ethnicity NTA		Unknown	
	estimate	% of total	estimate	% of total	estimate	% of total	estimate	% of total	estimate	% of total
1994	7,360	79.0	915	9.8	343	3.7	---	0.0	616	6.6
1995	7,451	76.9	793	8.2	504	5.2	—	0.0	821	8.5
1996	9,112	79.[illegible]	535	4.7	577	5.0	235	2.0	961	8.4
1997	9,425	81.5	768	6.0	517	4.5	47	0.4	813	7.0
1998	10,710	78.7	904	6.6	856	6.2	—		1,042	7.6
1999	12,548	82.[illegible]	967	6.3	523	3.4	364	2.4	850	5.6
2000	15,871	79.0	1,375	6.8	1,083	5.4	220	1.1	1,549	7.7
2001	17,104	79.3	1,072	4.9	1,481	6.9	53	0.2	1,858	8.6

DAWM Medical Examiner's Data

The DAWN system also reports annual medical examiner data for drug abuse deaths. Table 15 lists the number of hydrocodone deaths reported to the DAWN system for the years 1992 through 2001. The number of hydrocodone deaths has been steadily increasing over the last decade.

TABLE 15. OFFICIAL DAWN ME DATA

YEAR	HYDROCODONE DEATHS	PERCENT TOTAL DRUG DEATHS
1992	100	0.93
1993	109	0.91
1994	131	1.06
1995	151	1.22
1996	179	1.44
1997	290	2.37
1998	294	2.86
1999	447	3.82
2000	548	4.84
2001	592	6.41
2002	618	6.12

Like the DAWN ED data, the ME data gathered from various municipalities indicate that some metropolitan areas are associated with high rates of hydrocodone deaths. Table 16 lists the top 5 metropolitan areas with the highest percentage of hydrocodone deaths.

TABLE 16 DAWN Medical Examiner Episodes for 2001; Ranking by SMSA (Standardized Metropolitan Statistical Areas)

RANK	SMSA	DEATHS	ALL DEATHS	PERCENT OF ALL DEATHS
1	NEW ORLEANS	81	329	24.6
2	LONG ISLAND	26	129	20.2
3	LAS VEGAS	60	376	16.0
4	BUFFALO	25	167	15.0
5	LOUISVILLE	10	83	12.0

In summary, DAWN data demonstrate that:

- The abuse of hydrocodone products has been escalating.
- Despite any deficiencies inherent in these data-bases, hydrocodone products are associated with significant drug abuse morbidity /mortality.
- Compared to codeine, a similarly controlled opiate analgesic, hydrocodone products are associated greater numbers of ED episodes even when data is normalized by prescriptions.
- Some municipalities have been associated with very high percentages of DAWN drug abuse episodes for hydrocodone.

Monitoring the Future (MTF):

Monitoring the Future (MTF), more commonly known as the high school survey on drug abuse, is a national survey funded by the National Institutes on Drug Abuse (NIDA) that provides data on drug use by 8th, 10th and 12th grade students. Starting in 2002, MTF added a question regarding non-medical use of Vicodin®. In 2002, 9.6, 6.9 and 2.5 percent of 12th, 10th and 8th grade students reported use of Vicodin® in the previous year. In 2003, those percentages increased to 10.5, 7.2 and 2.8 percent, respectively.

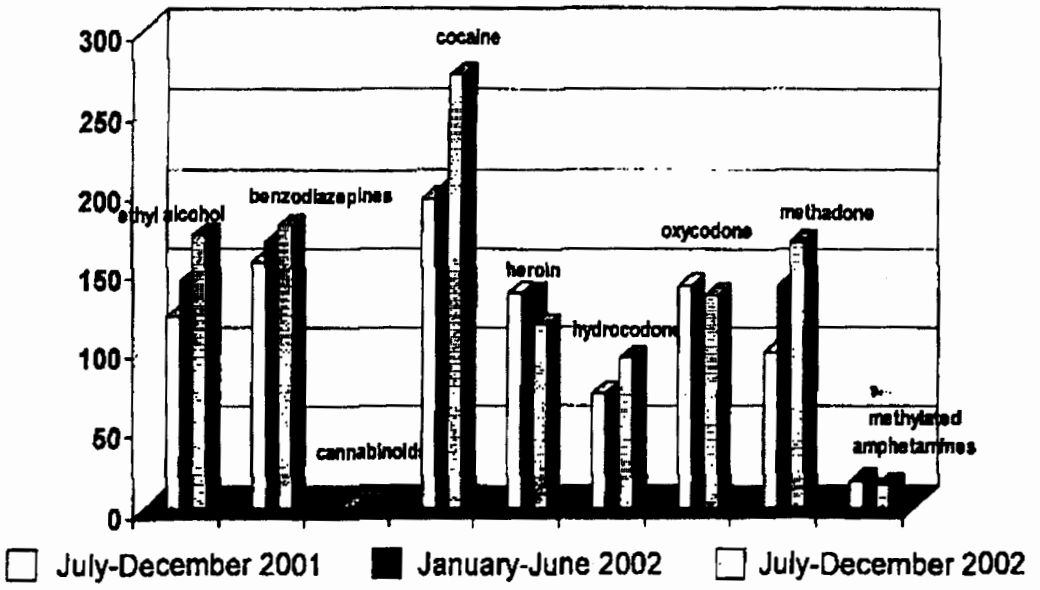
Other Medical Examiner Data:

The Florida Department of Law Enforcement publishes a yearly report detailing medical examiner's reports for drugs that were identified in deceased persons. In 2002, there were approximately 168,500 deaths in Florida. Florida medical examiners accepted jurisdiction of, investigated and certified 20,858 of these deaths. There were 15,676 deaths in which autopsies were performed and toxicology tests were conducted to determine the presence of drugs. There were 5,816 drug-related deaths based on toxicology reports. The state's medical examiners were asked to distinguish between the drugs being the "cause" of death or merely "present" in the body during the death investigation. Table 17 below summarizes Florida's drug related deaths from January through December 2002.

Table 17 2002 Florida Drug Related Deaths

DRUG	TOTAL DEATHS	CAUSE	PRESENT
Ethyl Alcohol	3,319	306	3,013
Benzodiazepines	1,625	346	1,279
Cannabinoids	682	0	682
Cocaine	1,307	427	880
GHB	19	6	13
Heroin	326	250	76
Hydrocodone	554	165	389
Ketamine	10	1	9
Methadone	556	308	248
Methylated Amphetamines	126	24	102
N2O	1	0	1
Oxycodone	589	256	333
PCP	1	0	1
Rohypnol	1	0	1

Florida ME Report July 2001-December 2002
Deaths in Which the Drugs Named Cause of Death



The graph above represents all Florida deaths from July 2001 through December 2002 in which various drugs were named as the cause of death. In the second half (July through December 2002), the number of deaths in which heroin was listed as the cause of death declined while both hydrocodone and methadone increased significantly. This may reflect the increased street availability of these pharmaceuticals due to the diversion of these medications from their intended medical use.

Hydrocodone-related deaths in Florida increased from 420 to 554 from 2001 to 2002, an increase of 32%. This was the largest increase for any drug except methadone. In 2002, 9% of the hydrocodone decedents were between 18 and 25 years of age, 12% were between 26 and 34, 48% were between 35 and 50 and 30% were older than 50.

Case Reports

The diversion and abuse of hydrocodone products is widespread. From October 2000 through February 2003, the DEA has conducted over 1,500 investigations involving hydrocodone products. These investigations have resulted in 373 arrests. Quarterly Reports submitted by all DEA Diversion Group Supervisors indicate that hydrocodone products are commonly diverted in every geographic area of the country and are the most sought after licit drugs throughout all 21 domestic field offices. Recent street prices average about $5 per tablet and have ranged from as low as $1 per tablet in Columbia, South Carolina to as high as $15 per tablet in Salt Lake City, Utah. Brand name products most frequently encountered on the street include Vicodin, Lorcet, and Lortab.

DEA case reports document the diversion of hydrocodone by pharmacy theft, doctor shopping, bogus call-in prescriptions, fraudulent or altered prescriptions, illegal internet purchases and diversion by registrants (see appendix for brief summaries of a sampling of case files). The following summaries are recent DEA cases involving hydrocodone diversion. While the DEA rarely encounters unscrupulous physicians, these cases involve significant diversion of hydrocodone products by physicians and demonstrate the potential damage a single "bad" doctor can do.

> A physician was arrested at Las Vegas International Airport carrying 30,000 tablets of hydrocodone. In a search of the physician's residence in Chicago, an additional 110,000 tablets of hydrocodone were found. A review of purchases made by this registrant over the previous 18 months revealed that this individual had obtained 549,000 tablets of hydrocodone. This physician had no patients in Chicago and was illegally delivering drugs to Las Vegas and shipping a large cache to the Philippines. The street value of the 549,000 hydrocodone tablets was estimated at about 2.8 million dollars in Las Vegas and between 11 and 15 million dollars (U.S.) in the Philippines.

> A physician was arrested by DEA in Florida on multiple drug-related charges. This physician was known throughout the community as a "script-doc". In exchange for a fee, this doctor would write multiple prescriptions for controlled substances and individuals could even purchase prescriptions in other people's names. The physician had recently sublet office space to a pharmacy whose sole purpose was to fill prescriptions written by this physician. In a one year period, this pharmacy dispensed 774,060 tablets of hydrocodone (as well as a number of other controlled substances). Medical examiners in neighboring counties have linked 30 hydrocodone-related deaths to prescriptions written by this physician.

Through numerous interviews and pharmacy surveys, evidence was collected showing that a West Virginia doctor was providing OxyContin and hydrocodone prescriptions to patients in return for sex. Patients involved in this activity were not only from West Virginia but numerous patients were traveling from Kentucky as well. This doctor was indicted on illegal drug distribution involving twelve patients. After a plea agreement, he was convicted of drug distribution and tax evasion charges and sentenced to fifty one months in jail. Following his arrest, further investigation determined that the doctor's nurse was continuing to distribute hydrocodone prescriptions. She pled guilty and was sentenced to 36 months active probation.

Other Data Sources

While there is no unified state data-base which monitors the diversion of controlled pharmaceuticals, some individual state offices have contacted the DEA to describe the severity of the hydrocodone abuse problem within their state:

- ***North Carolina Department of Health and Human Services***: In the decade of 1990 to 2000 the state of North Carolina reported that 460,848 dosage units of hydrocodone-combination products had been diverted or reported stolen within the state.
- ***Kentucky Department of Health Services:*** In 1998 there were 86,994 dosage units of hydrocodone-combination products diverted in the state of Kentucky; by 1999 the diversion rose to 299,300 dosage units. The Pharm-Alert system within the state reported that in 1998 hydrocodone-combination product mentions made up 37.6% of the total alerts, while in 1999 hydrocodone mentions rose to 59.0% of all mentions in the state. Doctor Shopper investigations involving hydrocodone rose from 40% of all investigations in 1998 to 57% in 1999.
- ***New Hampshire Board of Pharmacy***: In 1999 hydrocodone-combination product "scams" constituted over 60% of all cases handled by the state of New Hampshire. "Scams" were defined as bogus telephone orders, Dr. Shoppers, stolen Rx blanks, forged or altered prescriptions, internal theft, impaired practitioners, and drug "tampering".
- ***South Carolina Department of Health***: In 1998 the Bureau of Drug Control conducted 308 investigations leading to arrest for hydrocodone diversion; in 1999 there were 247 investigations.

- ***Hawaii's Narcotics Enforcement Division:*** The department investigated 64 cases of hydrocodone diversion in 1998 and 69 cases in 1999. The majority of these cases were fraudulent prescription and multi-doctor cases.
- ***Ohio: State Board of Pharmacy and Cincinnati Police***: The state of Ohio's pharmacy control board reported that they investigated 65 cases of diversion of hydrocodone-combination products (defined as theft, deception, illegal procurement, and trafficking) in 1997, 145 cases in 1998, and 158 cases in 1999. As reported by the Cincinnati Police Department, since 1990, hydrocodone was ranked as the number one prescription drug diverted in their area. Over 699,300 tablets, having a street value of about $6.00 per tablet, were confiscated in the Cincinnati jurisdiction from October 01, 1990 through May 31, 2003.

The Community Epidemiology Work Group Report to the National Institute on Drug Abuse has included a yearly summary of hydrocodone abuse (CEWG, 1996, 1997, 1998, 1999, 2000, 2001, 2002). A summary of these reports for hydrocodone include:

1996
Hydrocodone remains readily available in Dallas, where it costs $1-$5 per tablet. Abuse of hydrocodone, particularly with carisoprodol, is also reported in Phoenix and Detroit. The drug is highly abused in New Orleans, where it sells for $10 per dose unit. Treatment providers in Boston indicate that diverted hydrocodone remains widely available and is often used in conjunction with heroin (p. 50).

1997
Hydrocodone and its combination products (Vicodin, Hycodan, and Lortab) are the primary narcotic controlled substances being diverted in Texas. Many pharmacists in that State have chemical dependency problems involving hydrocodone in combination with benzodiazepines. In Arizona hydrocodone accounted for more than 40 percent of forged prescriptions (schedule III and V), according to the DEA's "Fax Net" (p. 44).

1998
Hydrocodone diversion is reported in New Orleans, Phoenix, Seattle, and the State of Texas (where it accounts for 80 percent of the diversion cases). The Seattle street price is stable at $3-$5 per tablet (p. 48).

1999
Hydrocodone is reported to be one of the most commonly diverted pharmaceutical opiates in several areas, including Boston, New York, New Orleans, and parts of Texas. Despite low indicators in New Orleans, hydrocodone abuse and fraudulent prescriptions are up, according to law enforcement sources. An ethnographer reported that it is also a common prescriptive drug of abuse in San Francisco (p. 53)

2000
Hydrocodone's street availability in New York City may be increasing. In New Orleans, along with oxycodone and propoxyphene, it remains the drug of choice among some users. In Massachusetts, pharmacy break-ins have increased recently, and police reported seizures of stolen hydrocodone (and oxycodone) on the streets. In Dallas, where it costs $4-$7 per tablet, and Houston, where it costs $3-$3.50 per tablet, it is one of the most commonly abused prescription drugs. (p.89)

2001
While the numbers of hydrocodone and oxycodone ED mentions tended to be small, they have been increasing in most CEWG areas. In 2000, the highest numbers of hydrocodone mentions were reported in Dallas, Detroit, Phoenix, St. Louis and Atlanta (p.28)

2002

Hydrocodone abuse indicators increased in most CEWG areas. Hydrocodone exhibits have increased significantly in the Miami crime lab. Increased deaths associated with hydrocodone consumption were reported in Detroit, Miami, Minneapolis/St Paul, Philadelphia, and Texas (p.19).

Factor 1 Summary:

- Hydrocodone has an abuse liability similar to morphine. It is self-administered in animal models, will substitute for morphine in drug discrimination studies and produces effects that are substantially similar to morphine in both animals and humans. Hydrocodone is equipotent to morphine with respect to subjective effects, opiate signs and symptoms and "liking" scores.

- Hydrocodone combination products are the most prescribed pharmaceutical opiates in the U.S. with over 111 million prescriptions dispensed in 2003. The most frequently dispensed combination product is hydrocodone + acetaminophen (approximately 80 % of all dispensed

hydrocodone products are in combination with acetaminophen). This combination carries additional drug abuse risks (see Factor 6). While hydrocodone products have been available in the U.S. for over a half a century, only recently have hydrocodone products become extensively used in pain management rather than cough suppression.

- A review of drug abuse indicators over the past several years indicates that hydrocodone has become a significant drug of abuse. In every geographical area in the country, the DEA has listed this drug as one of the most commonly diverted drugs. Law enforcement has documented the diversion of millions of dosage units of hydrocodone by theft, doctor shopping, fraudulent prescriptions, bogus "call-in" prescriptions and diversion by registrants and Internet fraud.
- DAWN data indicate that hydrocodone abuse is associated with considerable morbidity/mortality. Hydrocodone was ranked 6th among all controlled drugs in the most recent (2002) ED DAWN data. Most of the 21,567 estimated ED episodes for hydrocodone in 2001 were associated with individuals that were taking the drug for dependence or suicide. Poison control data, DAWN ME data and other medical examiner data indicate that hydrocodone deaths are numerous and wide spread.
- Monitoruing the Future data indicates the a substantial percentage of young Americans have access to hydrocodone and use it non medically.
- Collectively, the data suggest that the addition of other drugs to hydrocodone, does not reduce the abuse potential of these products.

FACTOR 2) SCIENTIFIC EVIDENCE OF ITS PHARMACOLOGICAL EFFECTS:

The early German reports compared the analgesic efficacy and potency of hydrocodone (Dicodid) to morphine. Castelhun & Langheinrich (1924) obtained complete sedation of cough with hydrocodone in all of their cases and the effect of hydrocodone on pain was equal to that of morphine, both as to degree and duration of effect. Kleinschmidt (1923) reviewed 250 cases of

pre- and post-operative use of hydrocodone (Dicodid) for analgesia. He concluded that 15 mg of Dicodid was equivalent to 10 mg of morphine when both were adminstered subcutaneously. Schindler (1923) reviewed 21 cases in which hydrocodone (Dicodid) was prescribed for "severe pain". Schindler reported that 10 mg of hydrocodone was equivalent to 10 mg of morphine when both drugs were administered subcutaneously. Schindler also demonstrated that hydrocodone produced less respiratory depression and nausea when compared to morphine. Herz (1924) reported that hydrocodone was "at least equal to morphine" for pain relief, when administered orally. In 1943 Krueger, Eddy, & Sumwalt translated and reviewed the early German reports relating to hydrocodone's analgesic effects - analgesia had been demonstrated with orally- and subcutaneously- administered doses as low as 5 mg; successful pain control had been achieved with a dose range of 5 to 20 mg. Reynolds & Randall (1959) claimed that a dose of 15 mg of hydrocodone is equivalent to 10 mg of morphine for pain relief in humans.

Eddy & Reid (1941) examined the analgesic effects of a number of opiates in cats. Thirty cats were tested for analgesia by applying pressure to the terminal portion of the tail and recording the latency of the animal to respond. The minimal effective dose, defined as that amount of drug which caused in at least four of the five animals receiving that dose an increase in the pressure required to evoke a response, was 0.75 mg/kg for morphine and 1.28 mg/kg for hydrocodone (expressed as the base). The duration of analgesia was the same for both morphine and hydrocodone (5 hours). Hydrocodone was reported to produce less emetic effects than morphine. Eddy, Halbach, & Braenden (1956) compared a number of opiates for analgesia and addiction liability. They reported a mouse analgesic ED_{50} for subcutaneously administered morphine of 2.1 mg/kg and for hydrocodone an ED_{50} of 3.2 mg/kg. They also reported that 50 mg of hydrocodone was equivalent to 50 mg of morphine for the maintenance of morphine dependence and that 15 mg of hydrocodone was equivalent to 10 mg of morphine for analgesia, in man.

More recently, Lelas, Wegert, Otton, Sellers, & France (1999) clearly demonstrated that hydrocodone was more potent than morphine in the tail-immersion antinociceptive assay in rhesus monkeys. Monkeys were tested in 40, 50, and 55° C water. The tail-withdrawal latencies under control (undrugged) conditions were 20, 1.42, and 0.79 seconds for 40, 50, and 55° C water, respectively. Hydrocodone was found to be 3.3 fold more potent than morphine in increasing tail-

withdrawal latencies; the ED_{50} values were 1.09 and 3.61 mg/kg for hydrocodone and morphine, respectively.

In their summary statement to the World Health Organization in 1957, Eddy, Halbach, & Braenden concluded that as an analgesic, hydrocodone was less potent than morphine, but that this was further offset by an addiction liability "almost as great as for morphine", when the dosage required for an analgesic effect is used. Further, Eddy, Halbach & Braenden concluded that "the duration of its effects was not materially different from that of morphine" (p. 600).

As translated by Hopkinson (1978a, b), Kenner concluded that 5 mg of hydrocodone was equivalent to 30 mg of codeine when administered orally (Kenner, 1930). Stein and Lowy (1946) reported that hydrocodone produced no euphoria, was less constipating than codeine and produced none of the adverse effects commonly observed during codeine administration. In contrast, Nathan Eddy had later demonstrated that a 5 to 10 mg dose of hydrocodone induces mild euphoria (cf White et al., 1941; Eddy et al., 1957). In 1938, Small *et al.* conducted a series of studies for the National Research Council at the University of Michigan Laboratories. Codeine was found to be less potent than hydrocodone on the following assays:

	Codeine (mg/kg)	**Hydrocodone (mg/kg)**
LD_{50} for ***mice*** after *s.c.* administration	241	86.0
Induction of convulsions in ***mice*** (s.c.)	161	47.0
General Depression ***(rats)***	38.1	4.20
Analgesia (tail pinch, ***cats, i.m.***)	8.04	1.28
Excitation (in 2 of 5 ***cats)***	8.04	0.86
Emesis (***cats***)	16.0	2.56

A number of studies have been conducted to compare the analgesic efficacy of codeine and hydrocodone. Using a tail-flick latency procedure to assess nociception in rats, Hennies *et al.* (1988) reported that hydrocodone and codeine were equally effective in providing analgesia, but

hydrocodone was more potent. Similarly, Hopkinson (1978a) reported that 10 mg hydrocodone and 60 mg codeine provided similar relief from postartum (episiotomy) pain. These data are interesting because Roller (1924) previously provided evidence that 5 mg of hydrocodone was equi-effective to 30 mg of codeine. The data from Hopkinson (1978a) and Roller (1924) may suggest a simple linear efficacy relationship between these two drugs. Hopkinson (1978b) additionally reported on a comparison between two combination products Vicodin (5 mg hydrocodone + 500 mg acetaminophen) and Tylenol #3 (30 mg codeine + 300 acetaminophen) for postpartum (episiotomy) pain relief. Hopkinson concluded that the Vicodin product provided better pain intensity relief (PID scores) when compared to the codeine combination product. When making direct comparisons of the parent compounds, these data must be viewed with caution since the amount of acetaminophen, a compound with analgesic properties, differed between the two combination test products. Beaver (1984) has presented data based on his previous work (Beaver & McMillan, 1980) which supported Hopkinson's (1978a) report showing that 10 mg hydrocodone was equally effective in pain relief to 60 mg codeine.

Forbes *et al.* (1981) demonstrated similar pain relief from oral surgery using Vicodin (5 mg hydrocodone + 500 mg acetaminophen), Tylenol #3 (30 mg codeine + 300 acetaminophen), and with the Emprin + Compound with Codeine (30 mg codeine, 227 mg aspirin, 162 mg phenacetin, 32 mg caffeine). A slight advantage in analgesic efficacy for post-oral surgery pain was later reported by Forbes *et al.* (1994) for a combination product containing 7.5 mg hydrocodone + 500 acetaminophen compared to a mixture of 30 mg codeine + 300 mg acetaminophen. Based on the previous studies described above, showing a 1:6 potency difference between hydrocodone and codeine, these data should not be surprising. In all of the studies just reviewed both codeine and hydrocodone were found to be superior to placebo.

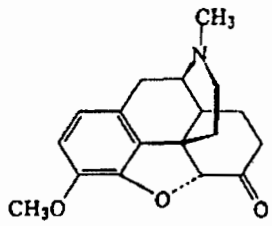
The efficacy of hydrocodone for the treatment of moderate pain has been repeatedly demonstrated. However, since the 1970 legislation which scheduled hydrocodone, newer nonsteroidal anti-inflammatory drugs (NSAIDs) have been developed which may be equally effective in the treatment of pain and prove to be safer based on the low dependence- and abuse-liability for these types of drugs. Recent comparisons between hydrocodone and ketorolac (a NSAID) demonstrated that both drugs were equally effective in the treatment of pain after

arthroscopic surgery (White *et al.*, 1997). Barber & Gladu (1998) have also compared the analgesic efficacy of ketorolac (20 mg) and hydrocodone + acetaminophen (10 mg + 1,000 mg) for the treatment of pain from arthroscopically assisted patellar-tendon autograft anterior cruciate ligament reconstructive surgery. There was a significantly better pain relief with the ketorolac than with hydrocodone treatments. In 1998, Innes *et al.* demonstrated that ketorolac had comparable efficacy to a codeine-acetaminophen combination product for the treatment of acute low pack pain in emergency rooms. However, ketorolac had a superior adverse event profile.

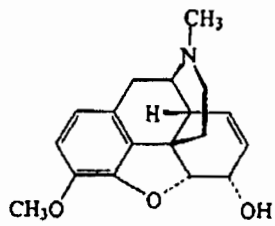
In summary, hydrocodone's pharmacological effects are similar to other mu opioid agonists. It is effective as an antitussive agent and as an analgesic for the treatment of moderate to moderately severe pain. In a majority of the standard behavioral assays, hydrocodone has been found to be more similar to morphine, hydromorphone, and oxycodone than to codeine.

FACTOR 3) THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCES:

Hydrocodone [4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5), dihydrocodeinone] is a semi synthetic opioid structurally related to codeine and is approximately equipotent to morphine in producing opiate-like effects (Jasinski & Martin, 1967; Fraser & Isbell, 1950). The chemical structure of hydrocodone and codeine are displayed, below:



hydrocodone



codeine

As shown in the structural figures above, hydrocodone lacks codeine's unsaturated C7-C8 bond, and the C6 position is occupied by a keto group instead of the hydroxyl group. This keto group at the C6 position is also found in the molecular structure of other narcotic agonists and antagonists. Stereoselective reductions of the C6-keto group of these substances have been reported (naltrexone: Cone *et al.*, 1974; naloxone: Roerig *et al.*, 1976; and hydromorphone: Cone *et al.*, 1977). Changes at the C6 position of the morphine molecule generally strengthen the potency of a morphine derivative, thus intensifying the characteristic physiological and toxic opioid action, while at the same time shortening the duration of the drug effects (Stein & Lowy, 1946). The structural difference between codeine and hydrocodone, at the C6 position, means that hydrocodone does not undergo the extensive conjugation (>60%) that codeine undergoes (Chen *et al.*, 1991). However, similar to codeine, hydrocodone has a C3 methoxy group on the aromatic ring which is available for O-demethylation.

The biotransformation pathways for codeine and hydrocodone are similar in both animal and man (Cone *et al.*, 1978, 1979). A 10 mg dose of hydrocodone administered to normal adult males (approx. 0.14 mg/kg) yields a mean peak plasma concentration of approximately 24 ng/ml. Hydrocodone concentrations show a first-order rate of decay and a half-life of 3.8 hrs (Barnhart, Caldwell, 1977; Cone *et al.*, 1978). Each type of metabolic transformation of either codeine or hydrocodone presumably can result in the production of an active metabolite. In a comparative analysis of the metabolism of hydrocodone, Cone *et al.* (1978) found that 50% of the total drug recovered from urine of man remained as hydrocodone which represented approximately 11% of the administered dose. The remaining half was divided among the following metabolite concentrations in descending order: nor-hydrocodone > hydromorphone > 6β hydroxycodol = 6α-hydroxycodol > 6β-hydroxymorphol > 6α-hydroxymorphol. The N-demethylation of codeine produces nor-codeine, and the same process in hydrocodone's metabolism produces nor-hydrocodone (Cone *et al.*, 1978, 1979). The pharmacological activity of nor-hydrocodone is not known, however nor-codeine is behaviorally active (Fraser Isbell, & VanHorn, 1960). Relative to codeine, hydrocodone is very lipophilic which may provide greater access of hydrocodone to N-demethylation. The Cytochrome P450 system, the major xenobiotic metabolic pathway, is responsible for the second biotransformation of these opioids. Specifically, the iso-enzymes 2D6 (man) and 2D1 (rat) are responsible for the 0-demethylation of codeine to morphine (Yue *et al.*, 1989; Mortimer *et al.*, 1990) and the 0-demethylation of hydrocodone to hydromorphone (Otton

et al., 1993; Tomkins *et al.*, 1997). The endogenous production of morphine from codeine and of hydromorphone from the degradation of hydrocodone has been suggested to be principally responsible for the pharmacological effects of each of these agents. This conclusion however, is equivocal at best and is not supported by existing data (see below). The 6-keto reduction products of hydrocodone are behaviorally active but lack stereoselectivity in man (Cone *et al.*, 1978) and seem to be short-lived.

The μ-opioid receptor binds agonists such as morphine, hydrocodone, and codeine. The μ receptor has been found to mediate the anti-nociceptive actions of such drugs. Morphine has been generally regarded as the reference compound against which other analgesics are assessed (WHO, 1972). A drug's affinity for binding to the μ-type receptor has been used as a relative marker for the effectiveness of opioid derivatives to produce analgesia and to rank order their relative potential for abuse (Jaffe & Martin, 1990). Using comparative tail-flick latencies in the rat as a measure of analgesia, the correlation between μ-receptor binding and ED_{50} values for analgesia for hydrocodone has been reported to be 0.883; the correlation between the opioid binding and antitussive effects is slightly lower 0.638 (Hennies, Friderichs, & Schneider, 1988) . In 1991 Chen, Irvine, Somogyl, & Bochner measured the relative affinities of a large number of opioid compounds to displace or inhibit tritiated [Tyr-*D*-Ala-Gly-*N*-Methyl-Phe-Gly-ol] enkephalin (^{3}H-DAMGO) binding. The relative inhibitory constants (Ki) resulted in the following rank order of affinities for the μ-type opioid receptor: hydromorphone (0.6) > morphine (1.2) > hydrocodone (19.8) > oxycodone (47.4) > codeine (248.3). These data show that only hydromorphone and morphine bind with the μ-type opioid receptor with higher affinity. Only hydromorphone and morphine are potent analgesic agents (Jaffe & Martin, 1990). These data suggest that hydrocodone is clinically active, binds less avidly to the μ receptor and provides relatively less analgesia than either morphine or hydromorphone. Problems arise, though, when making relative assessments of analgesic efficacy since codeine (248) has approximately 1/10th the affinity for the μ-type opioid receptor compared to hydrocodone (19.8), yet most of the comparative studies on these agents have demonstrated equi-effectiveness as analgesics (see below). In addition, recent data from Lelas *et al.*, (1999), described above, demonstrated that hydrocodone was more potent than morphine in the tail-immersion assay in rhesus monkeys.

An early proposal was made that the pharmacological effects of codeine were based on the *in vivo* production of morphine (Sanfilippo, 1948). Counter to this early proposal, studies conducted in the treatment of post-operative dental pain have shown that a second dose of codeine taken about 3 hrs after the first gives a threefold better analgesia than the first dose (Quiding, 1984). However, Quiding *et al.* (1986) also found: 1) that the morphine produced from codeine administration was only 2-3% of the administered dose, and 2) that the maximum plasma codeine concentration after the second dose was higher than the first dose, but the corresponding plasma concentrations of morphine were not increased. If analgesia is contingent upon morphine production, then it would be expected that the increase in analgesia after the second dose of codeine would be associated with an increase in morphine levels. But, this does not appear to be the case. Other data described by Way and Adler (1962) have further questioned the role of morphine in codeine's analgesic effects.

Similarly, one proposed mechanism underlying the abuse potential of hydrocodone is the pharmacological efficacy of the *in vivo* production of hydromorphone. The 0-demethylation of hydrocodone to hydromorphone is determined by the 2D6 iso-enzyme of the Cytochrome P450 (CYP 450) system. It has been determined that the CYP2D6 catalyzed hydromorphone formation is not a major metabolic pathway, a conclusion supported by the extremely low recovery of urinary hydromorphone after hydrocodone administration (approximately 6% of the dose of hydrocodone in one study (Otton *et al.*, 1993) and only 3.5% of the administered dose in another (Cone *et al.*,1978)). Additionally, deleterious mutations of the gene encoding the CYP2D6 enzyme occur in about 7% of the white population. These subjects, called poor metabolizers (PM), are distinguishable from extensive metabolizers (EM) by their inability to perform CYP2D6-catalyzed biotransformations. EMs and PMs do not differ in the urinary excretion of *endogenous* codeine or morphine (Mikus *et al.*, 1994). In pharmacokinetic studies poor and extensive metabolizers, while differing in their abilities to transform codeine-like drugs, do not significantly differ in the time of appearance of the O-demethylation by-products in blood plasma after parent-drug administration (t_{max} for EM: 1.0 hr ; for PM: 1.3 hrs; C_{max} values: EM: 12.4 nmol/L; for PM: 1.4 nmol/L; Fromm *et al.*, 1995). Previous pharmacokinetic studies in "normal adult males" demonstrated time to peak concentration of 1.3 hrs for the conversion of

hydrocodone to hydromorphone (Barnhart & Caldwell, 1977), a value similar to the Fromm *et al.* (1995) study. Additionally, no significant differences have been found between poor and extensive metabolizers of hydrocodone in either objective or subjective drug effects (Kaplan *et al.*, 1997). Subjective measures of hydrocodone using the Addiction Research Center Inventory (ARCI) profile of mood states (POMS) and a collection of rating scales, such as drug liking, anxiety, and nausea, demonstrated no group differences between the two phenotypically-derived groups of human subjects. If the *in vivo* formation of hydromorphone was a critical factor in the subjective effects of hydrocodone, such subjective-effects measures should have produced significant group-dependent differences. Additionally, in preclinical assays, rats were administered quinine - an active inhibitor of CYP2D1 (the rat homolog of the human CYP2D6). CYP2D1 inhibition had no impact on hydrocodone's analgesic, reinforcing, or discriminative stimulus effects. The effects of quinine-induced inhibition of the major enzyme responsible for the production of hydromorphone in the rat had subtle effects on the locomotor activating effects of hydrocodone which could not be separated from the effects of quinine administration alone (Tomkins *et al.*, 1997). France, Wegert, Otton, & Sellers (1996) examined the discriminative stimulus and antinociceptive effects of hydrocodone and hydromorphone alone and in the presence of inhibitors of the P450 isoenzyme in rhesus monkeys. Hydrocodone and hydromorphone had morphine-like discriminative stimulus effects and were fully-effective in a warm-water tail withdrawal assay of antinociception. Neither budipine nor quinidine, both inhibitors of CYP2D6, reliably altered the potency or the antinociceptive effects of hydrocodone and hydromorphone. The authors concluded that it was not necessary to convert hydrocodone to hydromorphone for the full expression of the behavioral effects of hydrocodone. In an analogous clinical study, administration of the CYP2D6 inhibitor, quinidine, to human subjects have replicated these preclinical findings in rats and monkeys and suggested only a small role of hydromorphone in eliciting abuse related responses to oral hydrocodone (Kaplan *et al.*, 1997). These data have been subsequently reconfirmed in rhesus monkeys by Lelas *et al.*, (1999).

Another opioid analgesic, oxycodone, is also metabolized by means of O-demethylation by the enzyme oxidation of P450 2D6 into oxymorphone. Similar to hydrocodone, oxycodone's abuse liability has been suggested to be dependent on the production of its metabolite, oxymorphone. Recent data by Heiskanen, Olkkola & Kalso (1998) has clearly demonstrated that

inhibition of P450 2D6 by quinine administration failed to substantially alter the pharmacodynamic effects of oxycodone and did not affect either its subjective or psychomotor effects.

Summary:

The above data indicate that hydrocodone's pharmacological effects, including analgesia, cough suppression, and other subjective effects (i.e., euphoria and drug liking), are most likely attributable to its own intrinsic efficacy at μ-opioid receptors. In addition, the data indicate that the *in vivo* production of its metabolite, hydromorphone, may not play a major role in the effects of hydrocodone administration.

FACTOR 4: ITS HISTORY AND CURRENT PATTERN OF ABUSE

Soon after its synthesis in Germany in the 1920s, reports started to emerge of hydrocodone addiction (cf Eddy, Halbach, & Braenden, 1957). In 1943, a comprehensive review of the German literature by Krueger, Eddy, & Sumwalt revealed a series of reports of hydrocodone addiction by Wolff (1928), Hoefer (1929), Richtzenhain (1931), Menninger-Lerchenthal (1931), Langelüddeke (1932), Meyer (1935), and by Pilcz (1937). In their report to the League of Nations in 1939, the Advisory Committee on Traffic in Opium and Other Dangerous Drugs reported that hydrocodone produced euphoria "but there is no doubt, as has been said before, that cases of addiction to Dicodid (hydrocodone) are known (p. 412)."

One of the first reports of abuse of hydrocodone in the United States was published in 1961 and described 45 cases of abuse in a district populated with less than 25,000 inhabitants (Rosenwald & Russel, 1961). In this early report, the physicians claimed that most of the criteria for narcotic addiction were fulfilled by each of the 45 abusers, each complained of dependence and withdrawal symptoms once the drug was removed and that relapse was common. They concluded their report by claiming that hydrocodone was an increasing substitute for the "higher narcotics."

Data regarding the pharmacological effects and abuse potential of hydrocodone were established well before the CSA was enacted and the placement of hydrocodone in Schedule II reflects that knowledge base. At that time, hydrocodone combination products were primarily utilized for cough suppression and were not widely prescribed. It was generally believed that the addition of other drugs to hydrocodone (within the parameters outlined for hydrocodone combination products in the CSA) and limiting the total amount of hydrocodone per dosage unit would mitigate serious drug abuse problems. Consequently, hydrocodone combination products were placed in Schedule III and or Schedule V, depending on the total amount of hydrodone per dosage unit. A similar rationale was used in exempting certain drug products from CSA regulations.

It was not until the 1990s that hydrocodone started to be widely used as an analgesic and also widely abused for its opiate effects. According to the DEA ARCOS (see Factor 1) the cumulative consumption of hydrocodone products has increased by about 700% since 1990. According to IMS, increased prescriptions of hydrocodone products are associated with the use of these products for pain management. Prescribing patterns associated with "bad" doctors indicate that individuals have taken large amounts (as many as 100 pills/day have been reported) to support their dependence and addiction.

Neither clandestine production nor illicit importations have played a role in the availability of hydrocodone in the U.S. With the exception of the recent exploitation of Internet sources for controlled substances [in particular lower scheduled drugs like Schedule IV benzodiazepines (Xanax®) and Schedule III hydrocodone products (Vicodin® and Lortab®)], the diversion of hydrocodone combination products from domestic sources is practically the sole source of this drug for abuse purposes. The appendix lists annotated case histories of a sampling of hydrocodone diversion cases characterized by DEA communications from its field offices from 1994 through 2002. These summaries reflect only those cases that were entirely federal or in which federal assistance was involved. The majority of cases involve diversion by health care professionals (nurses, doctors, pharmacists, etc.). In addition, these cases document a number of illegal activities including drug theft, "bogus call-in" prescriptions by individuals illicitly using DEA registration numbers, fraudulent prescriptions and various drug trafficking schemes. While these methods of diversion are not unique, the number of cases involving hydrocodone and the amounts of hydrocodone diverted from legitimate channels are significant. From October 2000

through February 2003, the DEA has conducted over 1,500 investigations involving hydrocodone products. These investigations have resulted in 373 arrests.

DAWN demographic data indicate that hydrocodone products (primarily pills) are usually taken orally and frequently taken in combination with alcohol. Most ED patients report that they have obtained hydrocodone from a prescription and have taken the drug to commit suicide or for drug-dependence. Of those patients that provided product-specific information, 81 % reported abusing Vicodin® and 17 % reported abusing Lortab®.

The DEA has received limited data from narcotic treatment centers. Data on hydrocodone treatment at publicly funded substance abuse treatment facilities is not available through TEDS (Treatment Episode Data Set). Hydrocodone was not listed among the drug choices on the form that clients use to report their drug use at time of admissions. However, the DEA did receive two independent reports from treatment centers in New York and Alabama indicating that 85% of all of their patients treated for opiate dependency in 2002 were hydrocodone abusers. In addition, the petitioner has provided data regarding patient admissions to his treatment facility. In 2002, the petitioner reported having 35 inpatient admissions for prescription drug dependence (hydrocodone products were listed as the primary or secondary drug of abuse in 18 of these admissions). In 2003, he reported having 39 inpatient admissions involving pharmaceutical drugs. A hydrocodone product was listed as the primary (19 patients), secondary (7 patients) or tertiary (1 patient) drug of abuse among those 39 admissions. According to the petitioner, it is not at all unusual for patients to report taking 40 to 50 tablets per day. The majority of the petitioner's patients were initially prescribed hydrocodone in good faith by physicians who where writing prescriptions for pain. According to Bingle et al. (1991) and Giannini (1997), the "medical" addict wittingly receives prescriptions from a licensed physician or dentist for the treatment of acute, sub chronic, or chronic pain. As tolerance to the drug develops the abuser escalates the dose upward. If cooperative or naive physicians are not available to continue writing the desired prescriptions, the medical addict will forge or steal prescription pads or buy diverted hydrocodone "on the street." The petitioner reported that most of his patients obtained their drugs through doctor-shopping, multiple visits to the emergency room and street purchases.

In summary, hydrocodone combination products are diverted and abused throughout the U.S. According to NFLIS and STRIDE (see Factor 1), hydrocodone products are the leading opioid pharmaceuticals submitted as drug evidence to federal, state and local forensic laboratories. DAWN data demonstrate that the abuse of hydrocodone products has escalated in the U.S. and the most recent statistics ranks hydrocodone as the 6th most frequently mentioned drug in ED episodes. Treatment centers have reported that a significant number of their admissions are involving hydrocodone products.

FACTOR 5: THE SCOPE, DURATION AND SIGNIFICANCE OF ABUSE:

In 1963, Dr. Nathan Eddy reported to the Committee on Drug Dependence that there had been outbreaks of hydrocodone abuse in various parts of the U.S over the preceding four years. Since that time, the abuse has continued and escalated although widespread diversion, trafficking and abuse of hydrocodone products were not evident until the 1990s. In 1992 and 1993, the United States report to the U.N. Drug Control Program (Annual Reports Questionnaire) documented a stable diversion of hydrocodone of approximately 200,000 dosage units per year. In 1994 the United States documented the diversion of hydrocodone at over 7 million dosage units for the year, and in 1997 the diversion rose to well over 11 million dosage units (data obtained from STRIDE exhibits and drug theft reports). The sharp increase in the diversion of licit hydrocodone suggests a pattern of misuse and abuse in the general population.

Today, hydrocodone-combination products are associated with significant illicit activity and abuse. Federal, state and local forensic laboratory data rank hydrocodone as the most frequently encountered opiate pharmaceutical in submissions to the laboratories. All twenty one DEA divisions across the U.S. have reported that hydrocodone combination products are among the most sought after licit drugs. From October 2000 through February 2003, the DEA conducted over 1,500 investigations involving hydrocodone products that resulted in 373 arrests. Millions of dosage units have been diverted by pharmacy theft, doctor shopping, bogus call-in prescriptions, fraudulent or altered prescriptions and diversion by registrants. In 2001, there were over 21,000 DAWN ED episodes associated with hydrocodone combination products and in 2002,

hydrocodone ranked sixth among all controlled substances. A number of data sources (See Factor 1) indicate that hydrocodone associated deaths in the U.S. are significant and increasing.

FACTOR 6: WHAT, IF ANY, RISK THERE IS TO THE PUBLIC HEALTH:

Despite hydrocodone's value as an antitussive agent and analgesic, the misuse and abuse of hydrocodone and hydrocodone products present a number of risks to the public health. Many of the risk factors associated with hydrocodone are common risks shared with other μ-opioid agonists. These include the risks of developing tolerance, dependence and addiction and the attendant problems associated with these risks. Other risk factors are particular to the hydrocodone and acetaminophen combination products that gain significance by virtue of being the most commonly prescribed and abused products in the U.S.

Hydrocodone's pharmacological effects, including analgesia, cough suppression, and other subjective effects (i.e., euphoria and drug liking), are most likely attributable to its own intrinsic efficacy at μ-opioid receptors. In a majority of the standard behavioral assays, hydrocodone has been found to be more similar to morphine, hydromorphone, and oxycodone than to codeine with an abuse potential equivalent to morphine. The prevalence of prescription drug abuse & addiction in the U.S. has been described elsewhere. It has been reported that 25% of all addicts die within 20 years of the initial usage (Preston & Jasinski, 1991). The financial cost of addictions is staggering; one estimate places the value at 67 billion dollars (Gold, 1997). These estimates include direct medical costs, lost productivity, injury, illness, as well as costs due to crime, motor vehicle accidents, and incarceration.

Liver pathology among opiate addicts is very common and its pathogenesis has been debated for years. It was formerly believed that the liver alterations were the result of previous viral infections, impurities, or alcohol abuse (Gorodetzky et al., 1968; Sapira, Jasinski, & Gorodetzky, 1968). However, experimental evidence has shown that opiates deplete glutathione levels (James et al., 1982), induce hyperglycemia (Feldberg & Shaligram, 1972) and elevate serum transaminases in animals (Chang & Ho, 1979) and the opiate-induced liver dysfunctions

usually are not accompanied by the changes in gamma globulin seen with viral infections. Clinical studies have documented liver dysfunction attributed to all of the opiates (see below), and have suggested that opioids may be intrinsic hepatotoxins and point to the potential risk of hepatotoxicity for humans after chronic therapy or self-administration (Gómez-Lechón et al., 1987).

No analysis of the deleterious effects of hydrocodone would be complete without reference to acetaminophen toxicity. The most common products containing hydrocodone also contain a therapeutic dose of acetaminophen. For example, Vicodin® contains 5 mg hydrocodone plus 500 mg of acetaminophen, Vicodin ES® contains 750 mg of acetaminophen in combination with 7.5 mg of hydrocodone, and Vicodin HP® contains 660 mg of acetaminophen plus 10 mg of hydrocodone.

At the 1999 annual meeting of the American Otological Society held in Palm Desert, California, Rick Friedman and colleagues presented evidence of profound hearing loss associated with hydrocodone/acetaminophen (Vicodin) abuse. The report presented 12 cases of patients experiencing a rapid progressive hearing loss and a concurrent history of hydrocodone + acetaminophen overuse. None of the patients experienced improved thresholds after high dose prednisone treatments. Eight patients underwent cochlear implants as a result of the drug-induced hearing loss. The hair-cell damage in the cochlear has been linked to oxidative-stress damage resulting from the acetaminophen content of the hydrocodone combination products. These results were recently published in the American Journal of Otology (Friedman, House, Luxford, Gherini, & Mills, 2000) and replicated by Oh, Ishiyama, & Baloh (2000).

The abuse of the majority of hydrocodone products also represents the abuse of acetaminophen. While acute hydrocodone toxicity occurs at relatively high doses, acute acetaminophen toxicity can occur in some highly susceptible individuals after the daily consumption of as low as 3 g of acetaminophen. Vale & Proudfoot (1995) report that those who ingest several high "therapeutic" doses of acetaminophen (for example, 7.5 to 10 grams per day by an adult) for 1 or 2 days and those who take multiple minor overdoses over a short period of time may develop severe hepatic damage. The acetaminophen dosage required to produce toxicity is variable from one individual to another. Single doses of more than 7.5 g in adults and 150 mg/kg in children have been used to define risk, but the actual toxic doses are dependent on a number of

pharmacological and historical variables (Smilkstein et al., 1988; Prescott, 1983) including ethanol consumption, opiate or cocaine use, other drug use (desipramine, MAOIs, etc), and nutritional status.

The usual single adult dose of acetaminophen is 325 to 650 mg for adults. This dose may be repeated every three or four hours as necessary. If a dose of 650 mg is ineffective, higher doses probably would not afford satisfactory relief. The total daily dose of acetaminophen should ordinarily not exceed 3 g (Koch-Weser, 1976; Vale & Proudfoot, 1995). The usual adult dose of Vicodin ES® is one tablet every four to six hours. The total daily dosage recommendation of Vicodin ES® is to not exceed 5 tablets. When, and if, a patient administers 5 tablets of Vicodin ES® in one day his/her daily dose of acetaminophen results in 3.75 g. As listed in the Product Information Packet supplied by Knoll Laboratories, both tolerance and dependence have been reported to develop over repeated dosing with hydrocodone products. This may result in the escalation of doses administered by the patient to overcome the shortened duration of analgesia resulting from the development of tolerance. As the dose, or the number of pills, is increased so does the total dose of acetaminophen. The escalating dosing regimen of Vicodin® products thus may lead to acetaminophen toxicity and liver failure.

As reviewed by Lee (1995), acetaminophen primarily undergoes sulfation and glucuronidation in which a large water-soluble polar group is attached to a hydroxyl oxygen forming ether or ester linkages. However, acetaminophen is also metabolized by cytochrome P450 2E1 to N-acetyl-p-benzoquinoneimine (NAPQI) if the sulfation and glucuronidation processes are exceeded or if cytochrome P450 2E1 synthesis is induced. The NAPQI that is formed from cytochrome metabolism may bind covalently to cell macromolecules, thereby disrupting mitochondrial and possible nuclear function. The formation of the covalent bonding can be prevented if NAPQI can be detoxified by conjugation with glutathione. The conjugation of NAPQI and glutathione, through a series of steps, will generate mercapturic acid. Depletion of glutathione reduces this last defense against the formation of NAPQI and the resulting covalent bonding to intracellular adducts. Thus, any situation that leads to glutathione depletion will increase the toxicity of acetaminophen. Poor diets and alcohol abuse have been shown to deplete mitochondrial glutathione (Lee, 1995). More importantly, it has been known for many years that

narcotic addicts typically demonstrate liver dysfunction that cannot be attributed to chronic or acute hepatitis from dirty needles (Marks & Chapple, 1967; Thureson-Klein *et al.*, 1978; Chang & Ho, 1979). Fatty infiltration of the liver, hepatic enlargements, and elevated levels of serum transaminase have been found in both mice and rats implanted with sterile morphine pellets (Emmerson *et al.*, 71; Chang & Ho, 79). These changes are similar to those reported in narcotic addicts (Klein & Magida, 1971; Lee & Rees, 1977). Over the last decade it has been repeatedly demonstrated that opioid administrations produce a rapid and dose-dependent depletion of liver glutathione levels. All of the major opiates including morphine, heroin, meperidine, methadone, morphinone, LAAM, βFNA, propoxyphene, codienone and codeine have been shown to deplete liver glutathione (James, Goodman & Harbison, 1982; Larson, Hus, Takemori & Portoghese, 1993; Ishida et al., 1989; Gómez-Lechón et al., 1987). To date, hydrocodone's effects on hepatic glutathione has not been reported; however, the noted similarities in the metabolic pathways of hydrocodone and the other opioids, especially codeine, suggest that hydrocodone administration likely produces glutathione depletion, as well. The co-administration of acetaminophen and either codeine or hydrocodone may render the liver more susceptible to glutathione-depletion and the subsequent hepatotoxicity and necrosis. In their report, James *et al.* (1982) suggested that it is the glutathione depletion by opioids that is the more likely cause of the observed potentiation of drug-induced hepatotoxicities. Further, they proposed that the glutathione-depleting effects of narcotic compounds be given particular consideration during multiple drug therapy, especially when combined with other known hepatotoxins, such as acetaminophen (p 712).

The normal concentration of glutathione in liver in various animals, including man, is about 4 mM (Mitchell *et al.*, 1974). Liver necrosis occurs after doses of acetaminophen that deplete more than 70% of hepatic glutathione. Thus, normal individuals would be susceptible to acute acetaminophen poisoning at doses over 15 gm (4% of 15 gm dose = 4mM of metabolite), and patients with induced drug-metabolizing enzymes would be susceptible to doses as low as 10 gm (Mitchell *et al.*, 1974). Patients with a history of alcohol or narcotic abuse and/or poor nutritional states are susceptible at much lower doses. A therapeutic treatment line, based on the analysis of the relation between serial plasma acetaminophen concentrations and liver function tests in individual patients, have been introduced to adequately treat incidents of toxicity. Patients whose plasma acetaminophen concentrations lie above the line are at risk of severe liver damage

(arbitrarily defined as transaminase activities [ALT/AST] above 1000 IU/L), while those below it will almost certainly escape serious consequences. The treatment lines were accepted internationally in the 1970s. The nomogram joins plots of 200 mg/L at 4 hr and 30 mg/L at 15 hrs (the 200 line) on a semilogarithmic graph. More recently the U.S. has modified this line further to a "150 line", joining 150 mg/L at 4 hr and 30 mg/L at 12 hr (Vale & Proudfoot, 1995; Routledge *et al.*, 1998). Bridger *et al.*, (1998) have recently recommended that the nomogram be lowered to a "100 line" for those individuals with known risk factors for hepatotoxicity which would include those individuals with a history of chronic alcohol, opiate, or cocaine misuse, eating disorders, and enzyme inducing drugs. It can be assumed that hepatic necrosis will occur if the plasma acetaminophen half-life exceeds 4 hrs, and hepatic coma is a very real possibility if the half-life is more than 12 hrs (Prescott *et al.*, 1971).

The chronic abuse of hydrocodone-containing products may increase the incidence of opiate-induced liver pathology and increase the individual's susceptibility to acetaminophen-induced hepatic toxicity. Of the 14 cases of fatal exposures involving acetaminophen + hydrocodone products listed in the 1997 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System (Litovitz *et al.*, 1998) seven cases had quantified plasma acetaminophen levels. Five of the seven reported cases exceeded the 30 mg/L concentration level of the "150 line"; one case reported a 27 mg/L level; and the final case had an acetaminophen level of 18 mg/L.

In 1993, Csette & Sullivan reported three cases of fulminant hepatic failure induced by acetaminophen toxicity secondary to Vicodin use. Fulminant hepatic failure is an acute hepatic necrosis in a patient without chronic liver disease, in whom encephalopathy develops within 8 weeks of the onset of the disease. Two of the patients reported by Csette & Sullivan (1993) died as a result of the disease. McBride (1995) described ten cases of opioid/acetaminophen misuse and dependence which lead to hepatotoxicity within a four year period. In 6 of the cases described by McBride, the plasma level of acetaminophen was in excess of the normal therapeutic range (9 μg/ml); the most common forms of abnormalities were raised γ-glutamyltransferease (GGT; 7 cases) and mean corpuscular volume (MCV; 8 cases).

The reported daily consumption of opiate/acetaminophen products by some abusers seems to defy the normal physiological clearance abilities of the P450 microenzyme systems. Some

abusers have reported a consumption of as many as 200 tablets per day leading to the voluntary consumption of in excess of 65 g of acetaminophen per day without significant laboratory test results indicative of hepatic injury. A theoretical model of protection from hepatic injury during these high dose exposures has been recently proposed by Shayiq et al. (1999). In the proposed model, Shayiq et al. suggest that chronic consumption and the process of escalating dose titration in chronic abusers set into motion a shift in the bioactivation of the acetaminophen from centrilobular to periportal regions where CYP2E1 is not found, protective GSH is more abundant, and where cell-proliferative responses are better able to sustain repair. The shift in acetaminophen bioactivation in hydrocodone abusers may result in a less-intense covalent bonding that is more diffuse and spread uniformly throughout the abuser's hepatic lobe, most likely contributing to protection by delaying the early onset of liver injury that has been associated with centrilobular localization of the adducts. These bioactivation processes may be the underlying mechanism by which abusers of hydrocodone-combination products can endure years of high dose consumption with normal liver profiles.

Summary: Hydrocodone combination products are associated with several public health risks shared by other opioids including the development of tolerance, dependence and addiction. The acetaminophen combination products pose significant risks associated with the high-dose abuse of these drugs. When taken acutely, high doses of acetaminophen have been shown to cause liver damage and death. The most frequently encountered hydrocodone products on the illicit market contain acetaminophen. By virtue of Schedule III placement in the CSA (as apposed to Schedule II), regulators are telling the general public that these substances are less likely to be abused. Call-in prescriptions and prescription refills contribute to the diversion and abuse of hydrocodone products thereby increasing the likelihood of harm to the public.

FACTOR 7: ITS PSYCHIC OR PHYSIOLOGICAL DEPENDENCE LIABILITY:

In 1943, a comprehensive review of the German literature by Krueger, Eddy, & Sumwalt revealed a series of reports of hydrocodone addiction by Wolff (1928), Hoefer (1929), Richtzenhain (1931), Menninger-Lerchenthal (1931), Langelüddeke (1932), Meyer (1935), and by Pilcz (1937). During the period from November 1949 through March 1950, the Committee on Drug Addiction and Narcotics of the National Research Council was called upon for evaluation and recommendations concerning the efficacy and dependence producing potential of hydrocodone and other narcotics. Hydrocodone was reviewed to be:

> in all respects morphine-like and, in spite of the chemical relationship to codeine, closer to morphine than to codeine in its dependence liability (p. 62, Eddy, 1973)

In one of the first set of comparative human studies conducted in the United States, Fraser & Isbell (1950) concluded that the total addictive liability of hydrocodone (dihydrocodeinone) "must be regarded as being more nearly comparable to the addiction liability of morphine than it is to the addiction liability of codeine (p. 134)." These data were subsequently supported by Jasinski & Martin (1967). These authors examined the abuse liability of morphine, hydrocodone and codoxime and reported that there was "no marked differences among the time-action curves of equipotent doses of the three drugs" (Jasinski & Martin, 1967, p 269). Relative potencies calculated and expressed as milligrams of hydrocodone equipotent to 1 mg of morphine sulfate were: 1.3 for pupil constriction, 1.0 for "opiate signs", 0.8 for opiate symptoms, 0.9 for "observers rating of 'liking'", 0.8 for "subjects liking, and 1.6 for abstinence suppression.

Hydrocodone bitartrate (dihydrocodeinone) was synthesized in the early 1920s and was shown to be an effective antitussive (anti-cough) and analgesic (pain relief) at doses as low as 10 to 15 mg (Hopkinson, 1978a,b). Early studies had demonstrated that the subcutaneous administration of hydrocodone was more effective than codeine as an antitussive agent. Throughout the 1920s twelve different studies, mostly conducted in Germany, concluded that hydrocodone was a potent and effective compound for the treatment of cough and pain (Crohn, 1923; Kleinschmidt, 1923; Schindler, 1923; Bing, 1924; Castelhun & Langheinrich, 1924; Herz, 1924; Roller, 1924; Schwab & Krebs, 1924; Rosenberg, 1925; Schammer, 1925; Schelenz, 1927;

Kenner, 1930). Hecht (1923) was one of the first to report that hydrocodone (Dicodid) produced a "striking euphoria" and habituation symptoms; his patients preferred hydrocodone to codeine and found it more effective in cough sedation than other antitussive agents he tested. Castelhun & Langheinrich (1924) obtained complete sedation of cough in all their cases and the effects of hydrocodone on pain were equal to that of morphine, both as to degree and duration of effect.

In their 1957 review to the World Health Organization on hydrocodone Eddy, Halbach, & Braenden reported on the addiction incidence and tests of addiction liability. Their report stated, that as far back as the 1920s, report of hydrocodone addiction were being made in Germany. Translated by Eddy, Halbach & Braenden the German reports were summarized as follows:

> As early as 1927 Müller de la Fuenta said that cases of addiction to dicodid were known; 17 of the 280 questionnaires analysed by Wolff in 1928 reported dicodid addiction; and in 1930 Richtzenhain warned that "dicodidismus" was then so often observed that one should be as cautious with dicodid injection as one would be with morphine.

The 1949 report of the 5th meeting of the Committee on Drug Addiction and Narcotics (one of the 15 medical advisory committees of the National Research Council) contains a summary of the work of Dr. Harris Isbell, Director of Research at the Lexington Kentucky USPHS hospital. Single acute tests of 30 to 40 mg of hydrocodone were assessed in 6 former opiate addicts. It was reported to the committee that all patients expressed satisfaction with the effects of the drug and were certain that they had received either morphine, dilaudid, or methadone. Evidence of euphoria persisted for as long as four hours after the injection. The committee's conclusions regarding dihydrocodeinone [hydrocodone, *sic*] were as follows:

> Because it produces unmistakable intense euphoria, because it will relieve the syndrome of abstinence from morphine, and because mild to severe symptoms of abstinence follow abrupt withdrawal of dihydrocodeinone after experimental addiction of 38 days duration, dihydrocodeinone must be regarded as possessing addiction liability which more nearly approaches the addiction liability of morphine than it does the addiction liability of codeine (*Bulletin, Drug Addiction and Narcotics*, by H. Isbell, *Appendix A*, 1949, p. 89 of report, p. 2 of Appendix).

Over the last few years there has been a growing number of Internet websites dedicated to discussions regarding hydrocodone addiction. The growth in treatment-focused websites and

chat-rooms supports the actual reports regarding Vicodin® dependence. Over months of Vicodin® abuse, the user experiences constipation, autonomic instability (periods of tachycardia & bradycardia), nausea and dizziness. As use continues, the abusers experiences blurred vision, hallucinations, and severe confusion. At high doses it induces respiratory depression. The withdrawal symptoms from Vicodin® abuse are equivalent to those described during withdrawal from morphine and heroin, including restlessness, muscle pain, bone pain, insomnia, diarrhea, vomiting, cold flashes, piloerection (goose bumps), involuntary leg movements, lacrimation, rhinitis, loss of appetite, irritability, panic, nausea, sweating. The severity of withdrawal from hydrocodone-containing pharmaceutical products is strikingly similar to the withdrawal symptoms expressed during morphine withdrawal. There appears to be little difference in the pattern of symptoms experienced with this combination product and symptoms associated with the abuse of any potent narcotic. The petitioner has also suggested that the dependence profile of hydrocodone combination products is no different than other Schedule II narcotics.

In summary, the data suggest that hydrocodone has a high potential for abuse and produces severe physical dependence. The data provided in Factor 1 and the data provided herein also suggests that there are no marked differences between the abuse potential and dependence profile of hydrocodone and hydrocodone combination products.

FACTOR 8: WHETHER THE SUBSTANCE IS AN IMMEDIATE PRECURSOR OF A SUBSTANCE ALREADY CONTROLLED UNDER THIS SUBCHAPTER:

Under the Controlled Substances Act of 1970, hydrocodone-combination products are placed in Schedule III. Hydrocodone bulk material is in Schedule II. Hydrocodone has been used as a starting material for the synthesis of thebaine by the legitimate pharmaceutical industry.

Abridged DEA Case Reports

(a random sampling of cases intended to show different types of diversion)

[redacted]

A female pharmacy technician was arrested for hydrocodone diversion. Using her cell phone the individual was calling in bogus prescriptions from a number of local pharmacies for personal use.

[redacted]

A female was arrested for fraudulently obtaining prescriptions utilizing her physician's DEA registration number and bogus "phone-in" prescriptions.

[redacted]

A pharmacist was arrested after a five month investigation for running a large scale internet pharmacy business and mail order pharmacy. The pharmacist diverted 300,000 dosage units of hydrocodone (among others) over a two year period. No valid prescriptions or physicians were utilized.

[redacted]

A male registered pharmacist was arrested for fraudulently filing fake prescriptions for 8,570 dosage units of hydrocodone.

[redacted]

A physician was indicted for writing hydrocodone prescriptions (among others) for other than legitimate medical purposes. Prescriptions for over 42,835 dosage units were written for other than legitimate medical purposes and were being illegally distributed through street sales.

[redacted]

A male physician was arrested for delivery of hydrocodone (570 dosage units of Vicodin ES) to patients with no medical complaint. Four separate purchases were monitored.

[redacted]

A female registered nurse was arrested for illegal distribution of hydrocodone. The nurse was removing hydrocodone from the intensive care unit and selling them out of her home.

[redacted]

A male pharmacist was arrested for delivery of hydrocodone without a valid prescription. Two purchases were witnessed of 160 dosage units and 400 dosage units, respectively.

[redacted]

A male veterinarian was arrested and voluntarily surrendered his DEA registration for ordering approximately 20,000 dosage units of hydrocodone and 249 bottles of hydrocodone syrup for personal use. The veterinarian admitted to consuming 65 tablets of hydrocodone per day.

A male physician was arrested for distributing hydrocodone from his office for no known medical reason. Most of the prescriptions written by the doctor were averaging 60 to 120 tablets per day per patient. The physician was averaging over 600 prescriptions per day. In one case he had written 39,281 dosage units for one patient.

A male dentist was arrested in a "sex for drugs" scheme with area "exotic dancers" and for self-abusing the hydrocodone, himself.

A female physician was arrested for obtaining hydrocodone (among others) for personal use. The doctor was writing prescriptions utilizing names of family members to obtain the narcotic. The doctor had concealed the drug use from her own physician who was treating her for lupus at the time.

A female licensed practical nurse was arrested for ordering hydrocodone for personal use utilizing the clinics DEA registration number. A large cache of opened and unopened bottles were found in the nurses locker and at her home.

A female office manager for a local physician was arrested for purchasing 16,300 dosage units of hydrocodone during a one year period. The manager was utilizing the physician's DEA registration number to order the drugs for delivery to the office and forging the physician's checks to pay for the drug delivery. The drugs were reportedly for personal use.

A male pharmacist was arrested for delivering 1,976 dosage units of hydrocodone to a local street level drug trafficker. The drug cache was intercepted. Seizure of the pharmacist's car revealed another 995 dosage units of hydrocodone.

A nurse practitioner was arrested for using her power of authority at the physician's office to coerce office assistants into calling in prescriptions for hydrocodone for her without the knowledge of the physician. Patient names or family members names were used and the nurse practitioner would pick the drugs up at the pharmacy for personal use.

A female was arrested for bogus "phone-in" prescriptions of hydrocodone for personal use.

A female pharmacy technician was arrested for passing forged prescriptions for hydrocodone. The woman stated that she was addicted to the drug and had stolen a prescription pad from an area physician. The technician was on bail from a previous arrest for similar forging of prescriptions for hydrocodone.

An owner of a group of weight loss clinics was arrested for employing physician interns to utilize their DEA registration numbers to dispense controlled substances. The owner was having physicians register at the clinics while none of the interns were licensed by the State of Louisianna to dispense controlled substances. The owner was in personal possession of 1,590 dosage units of hydrocodone (among others). A search of the owners home revealed another 14,928 dosage units of hydrocodone (among others). The owner was distributing the drugs for street sales.

A male pharmacist was arrested for stealing over 10,000 dosage units of hydrocodone (among others) over a 14 month period.

A male pharmacist was arrested for illegally obtaining hydrocodone by use of stolen prescription pads from three physicians in the area.

A male physician was arrested for illegally obtaining hydrocodone by using bogus prescriptions written for a 92 year old patient residing in an assigned living center. The doctor admitted self use of the hydrocodone. At the time, the physician was 'chief of staff' at the University of Arizona Medical Center.

A male pharmacist and owner of a pharmacy in the Houston area pled guilty to illegal delivery of hydrocodone. He was considered Houston's most prolific diverter of hydrocodone and the 8th largest volume hydrocodone purchaser in the United States.

A male high school teacher was arrested for selling hydrocodone to students for grades or sexual favors. The teacher acquired controlled substances by fraud, elderly abuse, and theft.

A male registered nurse was arrested for stealing and selling hydrocodone. The nurse admitted to taking half of the controlled substances designated for patients use in the intensive care unit. He stockpiled the tabs for future sale from his home.

A female pharmacist was arrested for personal abuse of over 70,000 milliliters and 1,000 tablets containing hydrocodone. The pharmacist would pay the token co-payment of prescriptions written for other patrons and use the drugs herself.

A female dental office assistant was arrested for fraudulent "phone-in" prescriptions in the name of some of the dentists' patients and picking them up for her own use .

A veterinarian was arrested for writing and acquiring prescriptions for hydrocodone which was being used by his addicted brother-in-law.

A male attorney was arrested for fraudulently writing prescriptions and acquiring the hydrocodone at pharmacies. The attorney ordered over 20,000 dosage units on 18 different occasions without the knowledge of his physician client.

A male physician was arrested for writing over 5,500 fraudulent prescriptions, totaling over 302,500 dosage units. Video taped evidence showed that the physician was providing prescriptions in exchange for sexual favors.

A male pharmacist was arrested for diverting and selling hydrocodone over a two year period. Two hundred hydrocodone tabs were sold for $750 on several occasions.

A male physician was arrested after writing hydrocodone presriptions for no legitimate medical reason during a series of undercover purchases.

A physician and two pharmacists were arrested for fraudulent medicare claims for treatment of non-existent conditions for the purpose of obtaining hydrocodone for sale. Multiple undercover purchases were made.

A male physician and attorney was arrested for selling over 5,000 dosage units per month of hydrocodone and other controlled substances. Approximately 40,000 dosage units were seized at the home along with $90,000 dollars in proceeds.

A male was indicted on 27 counts for obtaining over 2,500 dosage units of hydrocodone by traveling around the states of N.C., S.C., and GA and obtaining prescriptions under false pretenses from physicians and hospitals for the same "medical complaint". The drugs were intended for subsequent sale.

A physician and eight others were arrested for an estimated 15 million dollar health care scheme for writing postdated prescriptions for hydrocodone and mailing them to other individuals.

A male dentist pled guilty of misrepresentation and diversion of hydrocodone. The physician was writing prescriptions after revocation of his license to practice. He dispensed prescriptions for over 3,000 dosage units of hydrocodone for his own reported back and leg pain.

[redacted]

A female was arrested at a pharmacy after paying for two fraudulent prescriptions. The female was using a prescription pad she stole from her doctor's office to write prescriptions for her addiction to Vicodin.

[redacted]

Four individuals were arrested for selling hydrocodone which they obtained from prescriptions received at a neurology and pain clinic and were found selling the tablets in the parking lot of the facility..

[redacted]

The assistant director of an "impaired physician's program at a major hospital in Chicago surrendered his DEA registration after being arrested for falsely prescribing Vicodin for his addiction to the drug.

[redacted]

A male pharmacy technician was arrested for diverting over 130,000 dosage units of Vicodin.

[redacted]

A male physician was arrested for fraudulently prescribing hydrocodone in a "sex for drugs" scheme. The physician provided 5 prescriptions of hydrocodone, 100 tablets per Rx, in two different names to an undercover agent.

[redacted]

A female pharmacy technician was arrested for diverting hydrocodone from her employer.

[redacted]

A male pharmacy technician was arrested after video tapes showed him diverting hydrocodone for personal use. The pharmacy had already reported a loss of over 130,000 dosage units prior to this single arrest.

[redacted]

A male was arrested for intimidating an elderly physician into writing prescriptions for hydrocodone for his personal use.

[redacted]

A male pharmacy technician was convicted of diverting hydrocodone. The technician was ordering extra bottles of stock for personal sale for profit.

[redacted]

A female office manager for a physician turned herself into authorities after discovery of diversion of over 900 dosage units of hydrocodone (Vicodin) and over 100 dosage units of Lorcet for personal use.

[redacted]

A physician surrendered his DEA registration after being discovered of calling in prescriptions for hydrocodone "day after day". The prescriptions were dispensed in his wife's name. The daily

prescription was for 30 to 40 tablets a day. The phsyician would pick up the prescriptions without his wife's knowledge. The physician admitted to having a "30 pill a day habit."

A female registered nurse was arrested for fraudulent "phone in" prescriptions for hydrocodone from eight different pharmacies. The drugs were reported to be for "personal use".

A female was arrested for fraudulently receiving in excess of 130 prescriptions, primarily hydrocodone, over a 6 month period.

A pharmacy technician was arrested for stealing in excess of 900 dosage units from the pharmacy.

A registered pharmacist was arrested for illegally distributing hydrocodone to his girlfriend. A search warrant to her apartment revealed numerous bottles with the names of various customers at the pharmacy. The case was based on sex for drugs.

A pharmacist was arrested for illegally distributing hydrocodone with intent to sell more than 500 grams or more of the drug. He was distributing the drugs via the mail and FAXed prescriptions he knew were fraudulent.

A female pharmacy technician was arrested for stealing stock bottles of hydrocodone (among others) during a three week period. She sold them for $7 and $10 per tablet.

A dentist was indicted for misrepresentation and fraud for obtaining hydrocodone in other persons names for his own use. The dentist was using a stolen prescription pad taken from a physician colleague in the same office complex.

A male suspect was arrested for making a fraudulent prescription on his computer. He forged his doctor's signature and made out the prescription for his sister.

A female pharmacist confessed to diverting 150 to 200 dosage units of hydrocodone from Eckerd Drugs. The pharmacist diverted over 30,000 dosage units over a one year period.

Two criminal complaints were filed against two individuals for diverting hydrocodone from a pharmacy. A total of 37,000 dosage units were diverted in a 6 month period.

A pharmacy technician was arrested for dispensing hydrocodone without prescriptions. The technician would remove stock bottles from the shelf when she believed no one else was looking and sold them in the parking lot outside the pharmacy.

An owner of a pharmacy was arrested for sale of over 500 grams of hydrocodone and intent to illegally sell the drug via the postal system.

A registered pharmacist was arrested for theft and diversion of hydrocodone from his pharmacy.

A federal jury convicted a physician for illegal distribution of drugs including hydrocodone.

A medical office assistant was arrested and admitted to fraudulently "phoning-in" prescriptions for hydrocodone on five separate occasions.

An unemployed housewife was arrested and admitted to fraudulently "phoning-in" prescriptions for hydrocodone for both herself and her husband.

A male pharmacy technician was arrested for fraudulently prescribing hydrocodone on three separate occasions. The pharmacy tech used the DEA registration number of his ex-physician.

A male physician was arrested and charged with 2 counts of illegal distribution of a controlled substance without a legitimate medical reason. During the short period of the investigation the physician was responsible for diverting hundreds of dosage units of hydrocodone. The physician voluntarily surrendered his DEA license and prescription privileges at the time of his arrest.

Two male suspects were arrested for using doctor's names and DEA numbers to fraudulently obtain hundreds of dosage units of hydrocodone and other scheduled drugs from pharmacies, then using and distributing the controlled drugs to friends and associates. The two were charged with 13 counts of obtaining controlled substances by fraud

A male registered nurse, employed at the Veteran's Hospital, was arrested for knowingly acquiring possession of at least 350 tablets of hydrocodone as well as other drugs for his personal use.

A female was arrested and charged with twenty counts of obtaining controlled substances by fraud, mostly hydrocodone. The female posted bond and was released on bail. While out on bail the DEA

offices received information that the same female was using a physician's DEA registration number to obtain hydrocodone; while on bail from the original charges, the female had obtained an additional 240 dosage units of hydrocodone fraudulently by phone-in prescriptions

An investigation into the prescription practices of a medical doctor was initiated when the DEA was notified that the physician had been providing hydrocodone and alprazlam to an individual in exchange for sex. Under consensual telephone calls, the physician stated he was creating patient charts for individuals and falsifying laboratory work to complete the charts. During the investigation another individual was found who was providing the doctor with sex for hydrocodone. The physician had written prescriptions for approx. 312,000 tabs of hydrocodone and had purchases at least 8,000 tablets of hydrocodone from pharmaceutical distributors. Local prices of hydrocodone are $10 to $15 per tablet which could have yielded 3.2 to 4.8 million dollars.

A male physician was interviewed by DEA regarding prescription errors. During the interview the doctor confessed to writing prescriptions for three employees who would return the drugs to the doctor for his own personal use. He surrendered himself and his DEA registration to the investigators. The Denver office placed a code "1" on the DEA registration number. Charges are pending in Denver.

A female was arrested for posing as a nurse practitioner and utilizing a doctor's registration number to receive fraudulent prescriptions of Vicodin.

A male anesthesiologist from the University Health Sciences Center was arrested after he consented to a search of his home and two vehicles and the discovery of a number of controlled substances, including hydrocodone, were found. The doctor surrendered his DEA registration number and confessed to providing controlled substances to friends, family and neighbors without legitimate medical need. Charges are pending.

A male physician was charged with 14 counts of drug-related crimes; three counts of distributing hydrocodone cough syrup and Tylenol #4's, distributing Valium for non-medical purposes; and 11 counts of omitting material on required records.

A male registered pharmacist was arrested for unlawful distribution and dispensing of hydrocodone. A juvenile was interviewed after arrest for selling hydrocodone to other high school students. The juvenile worked at the K-mart where the pharmacist worked. Over a ten month period the pharmacist could not account for 1,766 hydrocodone tablets, 54 methadone tabs, 80 Ritalin tabs, and 144 Lortabs. The pharmacist confessed to distributing only 3 codeine tabs to co-workers to treat pain without the authorization of a physician. He also confessed to distributing drugs to co-workers by issuing prescriptions in his name, passing them through his insurance and splitting the prescriptions with his co-workers.

The chief pharmacist at a local hospital was arrested for possession of hydrocodone and for dispensing controlled substances without presciptions. A 16 month audit revealed shortages of 4,400 dosage units of hydrocodone (7.5 lortab), 4,600 Tylenol #4's, and 100 dosage units of vicodin. A 42 month audit revealed that an additional 1,770 Lortab and 1,453 Tylenol #4's may have been diverted.

A husband and wife were arrested for possession and intent to distribute controlled substances. The female was working as a pharmacy technician and was arrested leaving the pharmacy with hydrocodone, Lortab, and viagra. She was previously fired from a hospital pharmacy for similar offenses. She confessed to selling the drugs for profit. Her husband was arrested at their home after a warrant was executed. Numerous drugs were found in the home.

A physician was arrested for writing excessive amounts of controlled substances, primarily hydromorphone and hydrocodone. Undercover officers obtained prescriptions without presenting any medical complaint. As detailed in the medical record, the hydrocodone was prescribed "because the patient asked for it and it made him feel good". The physician has surrendered his DEA license. The owner of the medical center also wrote prescriptions on this physicians DEA number and is being investigated for Medicaid fraud and diversion, as well.

A physician and his wife were arrested for illegally distributing hydrocodone. The physician's DEA registration was revoked at the time of the distribution. He was prescribing Vicodin for family members, his wife would pick up the prescriptions, without the family members knowledge.

A registered pharmacist was arrested for possession and diversion of HC-tussive (hydrocodone) from a large chain pharmacy where he worked.

A male physician was arrested and subsequently lost his DEA license for writing prescriptions for money. Fifteen prescriptions were purchased by an undercover agent for $500. Other agents purchased 10 additional prescriptions for $400.

A male physician surrendered to officials for arrest on drug charges. The physician and three others ran a city weight clinic and diverted thousands of dosage units of Vicodin, Didrex, and methadone from the clinic. The physcian plead guilty to two counts and surrendered his license. Two co-defendents, a physician and ex-police officer are expected to enter similar pleas in the next few weeks.

An owner and sole pharmacist at a local drug store was arrested on 8 counts of unlawful possession with intent to distribute and 8 counts of intentionally omitting material information from required records. The pharmacist was selling large amounts of controlled substances. Under a reported threat of harm, the pharmacist stated he was being blackmailed to distribute drugs to one individual. The indictment charges that the pharmacist distributed in excess of 11,855 Vicodin/Vicodin ES (among other drugs) over a five year span. The "blackmail" excuse is being investigated but it is reported to contain many discrepancies.

A man was arrested for forgery, possession of a controlled substance, and diversion of prescriptions (among others). The man was a long time companion of a physician and was forging prescriptions to obtain controlled substances for a protracted time, even after the physician had died. The prescriptions included vicodin, percocet, didrex, seconal, and carisoprodol.

A psychiatrist signed a memorandum of agreement to pay a $12,500 fine for knowingly prescribing inappropriate amounts of controlled substances to known addicts. Under the guise of running a pain management clinic the psychiatrist was supplying large amounts of Vicodin, Percocet, and Dilaudid to known addicts.

A male physician was arrested for writing a series of presciptions for himself using other individual names and addresses (patients of his). He used his own phone number and physician's name.

A registered pharmacist was arrested for unlawful dispensation of hydrocodone. The pharmacist was using hydrocodone for payment to a janitor for cleaning services in the pharmacy. After being charged the pharmacist contacted one of the witnesses in an attempt him to change his testimony (witness tampering)

A female medical assistant was arrested for fraudulantly obtaining hydrocodone through bogus "call-in" prescriptions to a local pharmacy using her ex-employer's DEA registration number. State charges were filed.

Federal indictments were set down on an osteopathic physician after a nine year investigation. Seven counts involved the illicit dispensing of drugs, including hydrocodone. The IRS found the doctor's wealth to be several million dollars; the locations of his practice were so unclean and vermin infested that the facilities were immediately closed by a health representative.

A 47 yr old male was arrested for writing and processing forged prescriptions for hydrocodone tablets from a prescription pad at his family physician's office. The physician was unaware of the

diversion. Local charges were filed.

[redacted]

During an interview regarding a loss of 50 pints of hydrocodone/homotropine syrup, a pharmacist admitted to DEA agents of diverting the substance for personal use. State charges were filed.

[redacted]

A pharmacy technician was arrested outside of a Walmart store and charged with two counts of possession with intent to sell controlled substances and one count of felony retail theft. The young lady was video-taped removing medications from the pharmacy. From January 01 to 23 March the pharmacy tech had made three orders for hydrocodone from the manufacturer and had diverted 10-12 bottles of hyrocodone products (especially Lorcet 10/650).

[redacted]

DEA received intelligence that a 54 yr old male was a major distributor of hydrocodone in Broward and Palm Beach counties. The individual was arrested upon delivering 5 sealed bottles of hydrocodone (2,500 tablets) to an undercover agent. A search of the individual's vehicle revealed two additional sealed bottles of hydrocodone (1,000 tablets) and Xanax (1,000 tablets). During December an undercover agent had purchased three other sealed bottles of hydrocodone (1,500 tablets); one bottle was labeled and local offices are tracing the diversion from the provided information. This case involves a total of 5,000 hydrocodone tablets.

[redacted]

A male physician was indicted by a grand-jury for knowingly or intentionally refuse or fail to make, keep or furnish any record, notification, order form, statement invoice or information required under the CSA, namely by receiving and dispensing controlled dangerous substances unlawfully. A review of purchases established that the physician purchased a total of 39,144 tablets of hydrocodone (Lorcet) and a benzodiazepine (Lorazepam) and their generic equivalents (Lortab 10 mg: 17,244; hydrocodone 7.5: 200; Lorcet + 7.5: 100; Vicodin ES, 7.5: 600). The doctor could not produce any records for the receipt or the distribution of those controlled substances; nor could he tell the investigators what happened to those substances.

[redacted]

A male and female were arrested and charged with four counts of posession of hydrocodone and eleven counts of Medicaid fraud. The male would call in "bogus" prescriptions pretending to be a physcian and the friend would pick up the prescriptions and sell them to a third party. The prescriptions were being charged to Medicaid funds.

[redacted]

A medical assistant was arrested for illegally obtaining several prescriptions of 10mg hydrocodone + APAP tablets in patients names and having them delivered to the doctor's office or picking them up without the patient or doctor being aware of the prescription. The prescriptions were unwittingly charged to the patient's insurance company by the pharmacist.

A male physician was arrested after the doctor purchased and received 100 hydrocodone-containing tablets (Lorcet) from a prescription of a confidential source which the doctor was using for himself. Over a 10 month period the source had purchased 18 prescriptions for the doctor which including hydrocodone (Lorcet & Tussionex) and other pain (percocet) and anxiolytic medications (Xanax & Valium). The lawyer representing the physician told local DEA agents that the physician would surrender his medical and DEA registration licences immediately.

Two drug companies notified the DEA that a physician had ordered and received **150,000** tablets of hydrocodone in one month. The physician notified the FBI in Las Vegas when he discovered that his brother and an accomplice were using his DEA registration number to order drugs. The two ordered hydrocodone, anabolic steroids, and diazepam from drug companies. The drugs would be delivered to the physician's address to be picked up by the brother without the physician's awareness. They would be transported to California, packaged in small bags and shipped to an associate in Boston or in Laguna Nigel, CA. The brother was arrested, the physician has been cooperative and is believed not to be involved.

As part of a two year investigation warrants were served on a pharmacy to collect evidence against the pharmacist who had been suspected of improperly distributing controlled substances, including hydrocodone. The pharmacist would order by telephone "excessive" amounts of controlled substances, knowingly receive fraudulent prescriptions from street dealers and accept cash and electronic equipment for the purchases. The pharmacist also defrauded Medicaid. During a 10 month period, the pharmacist purchased and delivered 444 gallons of Tussionex. The search warrant uncovered counterfeiting evidence and the secret service was brought into the case, as well.

The diversion office received a letter from a pharmacy to report the termination of an employee for generating new controlled substance prescriptions for a patient without a physician's authorization. A total of 690 hydrocodone tablets were illegally dispensed over a period of 3 months using this technique. The pharmacy tech also deleted prescriptions from the computer files; 11 prescriptions totaling 440 tablets of hydrocodone were deleted from the files. An additional 7 prescriptions totaling 300 tablets was also discovered.

A 40 yr old male dental equipment repairman was obtaining various dentist's DEA registration numbers and patient information when he arrived at the offices to repair equipment. He called in prescriptions of hydrocodone and then pose as the patient using the information he picked up at the dentist offices. The individual was arrested during a purchase at a local drug store.

An ongoing investigation of a female who habitually uses bogus "call-in" prescriptions to obtain hydrocodone. This individual obtained at least 575 tablets of hydrocodone containing products (Vicodin, Lortab) from different pharmacies by using different physician's names and bogus prescriptions.

[redacted]

A 34 yr. old female was using a number of aliases under which she would use "call-in" orders from different physicians in the area. The suspect used a number of drug stores in the area to obtain hydrocodone by fraud.

[redacted]

An 18 yr old female pharmacy technician admitted to and was arrested for supplying hydrocodone to her sisters boyfriend without a prescription. The pharmacy tech would remove prescriptions from a pile of prepared prescriptions waiting to be picked up; she would have her friend drive by the 'drive-through' window and pass it to him. When the legitimate customer would come by to pick up their prescription she would search for it, notify the pharmacist it was not there, and they would re-issue the legitimate prescription to its rightful owner.

[redacted]

A former medical assistant (MA) to a registered physician was arrested for illegally obtaining the doctor's prescription pad. The MA wrote prescriptions for a male accomplice for hydrocodone. The MA used the physician's name and stamp signature. The MA admitted to writing two fraudulent prescriptions for her accomplice. Pharmacy records showed that four additional prescriptions were forged and processed dispensing a total of 520 hydrocodone tablets during a 3 month period. The MA was taken into custody after a bond reduction hearing for 1 count of trafficking hydrocodone. Through false prescriptions she fraudulently obtained, among others, 900 dosage-units of hydrocodone.

[redacted]

A female registered nurse was arrested for two counts of prescription forgery (state charges) which included hydrocodone. She was confronted by authorities and was found to have controlled substances in her possession in her purse including prescriptions for hydrocodone. The RN admitted to forging the prescriptions. She was released on bail and will be arraigned at a later date.

[redacted]

A male was arrested and charged with distribution of hydrocodone. On two occasions the individual sold stolen hydrocodone to a cooperative source. A subsequent search warrant resulted in seizure of 40 hydrocodone tablets, marijuana, money, a gun, and paraphernalia.

[redacted]

A veterinarian was arraigned on ten counts of obtaining possession of a controlled substance, hydrocodone, by misrepresentation, fraud, forgery, deception and subterfuge by writing prescriptions in the names of his animal patients. This investigation is ongoing.

[redacted]

A young female registered nurse was arrested on 13 counts of obtaining a controlled substance (hydrocodone) by fraud. This individual used "call-ins" to order prescriptions from a local Walgreen's pharmacy using a local physician's name and DEA registration number. A total of 180 tablets and 540 mls of hydrocodone containing products were illegally obtained by the RN over a two month period.

A pharmacy manager was indicted on one count of unlawfully, intentionally, and knowingly delivering a dangerous drug, hydrocodone, to special agent of the DEA. He pled no contest and was sentenced to one year suspended sentence, two years probation, and $300.00 fine.

A male veterinarian was indicted on three counts of obtaining controlled substances by fraud. The individual is not a currently licensed veterinarian in the state of Tennessee nor has he a DEA registration. The case was processed through a state indictment after the US attorney's office declined the case.

A dentist and his wife were arrested on 27 counts of obtaining Vicoprofen by fraud (among other charges). The dentist had previously surrendered his DEA registration for prescribing medications to himself and his wife for no medical purpose. The dentist was using his partner's DEA registration.

A doctor confessed to diverting quantities of hydrocodone for his own personal use from patients for a period of over one year. The doctor surrendered his registration and entered a no contest plea and was sentenced to 60 months state probation, $900 court costs, $2500 reparation fee, and 1,000 hours community service.

A female office manager at a doctor's office was arrested and charged with on count of hydrocodone possession (among others). The office manager utilized the doctor's prescriptions throughout the county. The elderly doctor was "being taken advantage" of by his live-in office manager. Additional charges are contemplated.

A male pharmacist technician was arrested for diversion of 4,500 dosage units of hydrocodone.

Two individuals were arrested for Vicodin associated diversions. One female was arrested for obtaining Vicodin by fraud, by using her ex-husbands registration number to obtain the drug. The pharmacist, who had been notified by the first individuals spouse that the prescriptions were not authorized continued to fill them. Both individuals were arrested.

A physician and a pharmacist were arrested for supplying controlled substances outside the realm of medical treatment. NDI investigators made 13 undercover purchases of prescriptions for hydrocodone products and other controlled substances. The physician owned the pharmacy and would provide prescriptions that he told the patients to fill at the family pharmacy.

A pharmacy technician was arrested for distribution of oxycodone (SCH II) and hydrocodone (SCH III) on three occasions

A woman was sentenced for illegally obtaining approximately 6,000 dosage units of hydrocodone by fraud.

A male pled guilty to two state counts of illegally obtaining Vicodin tablets by fraud and deceit. The individual called physicians in the area and claimed to be a dentist. He stated that a family member was in town and in need of pain medication until they could visit the doctor's office. The defendant allegedly obtained nearly 3,000 tablets by using the telephone to deceive 80 physicians in the New Orleans area.

A medical doctor pled guilty and was sentenced for distribution of Dexedrine, Percodan, Vicodin ES, and Valium. The prescriptions were issued outside the course of the usual practice of medicine and failed to keep complete medical records on the recipients of the prescriptions.

A physician was found guilty of 19 counts of unlawful distribution of Percocet (oxycodone) and 9 counts of unlawful distribution of hydrocodone (Lorcet and Vicodin) and benzphetamine (Didrex). The physician continued to prescribe medications even after surrendering her DEA registration .

A pharmacist and owner of a pharmacy was indicted on 7 counts. One count was for the distribution and dispensing of hydrocodone for other than legitimate medical purposes and outside the scope of professional practice near a school. Earlier, this same individual was arrested for illegal possession and distribution of a controlled substance.

A woman posing as a doctor's medical assistant was arrested on one count of unlawful acquisition of hydrocodone.

A medical doctor was arrested for state charges of obtaining hydrocodone, a controlled substance, by deception. The doctor had previously admitted diverting quantities of hydrocodone for his own personal use from patients for a period of over one year.

An individual pled guilty to one count of prescription forgery (120 forged prescriptions authorizing 190 refills for hydrocodone (Vicodin) and Klonopin). The diversion involved in excess of 3,000 dosage units.

A federal search warrant was served on a pharmacy in Murrysville, PA. Also served was a DEA Immediate Suspension of the pharmacy's registration. The pharmacy had been suspected of "large scale" diversion of hydrocodone (and alprazolam). An estimated 3,000 dosage units of Vicodin were diverted and approx. 20 other arrests are pending.

A dentist was found guilty of 8 counts of felony distribution. Vicodin-ES and Lorcet (both hydrocodone) were prescribed to cooperating patients/drug users who would pass the prescriptions on to pharmacies and then return to split the drugs with the dentist.

A registered pharmacist and owner of a pharmacy was sentenced for the illegal sale of 100 Vicodin (hydrocodone) tablets.

An individual pled guilty to diverting in excess of 7,000 dosage units of hydrocodone by use of falsified prescriptions

A licensed practical nurse (LPN) was arrested for ordering "phone-in" prescriptions in the amount of approximately 1200 dosage units of hydrocodone and phentermine. The LPN used the DEA registration number of her employer. The controlled substances were purchased for personal use and for the use of the LPN's daughter.

A registered pharmacist confessed to, and was subsequently arrested for, the diversion of 1,000 dosage units of hydrocodone. The hydrocodone was illegally dispensed in exchange for cocaine and "favors". The drugs were dispensed without a prescription.

A physician was convicted and sentenced for fraudulently obtaining in excess of 7,000 dosage units of Percocet and in excess of 53,000 dosage units of Vicodin (hydrocodone) for personal use.

A man plead guilty to knowingly and intentionally using the DEA registration number of his wife, a medical doctor, to obtain Lorcet (hydrocodone).

A 257 count federal grand jury indictment was handed down for a pharmacy owner for diverting thousands of dosage units of Hycodan and Alexsia (both hydrocodone). 15 associated defendants were also charged in the indictment. During the commission of the search warrant a number of unlisted individuals entered the pharmacy with fraudulent prescriptions to be filled; all were subsequently arrested.

[redacted]

A pharmacy technician was arrested after being caught on video tape stealing 100 tabs of Vicodin (hydrocodone).

[redacted]

A woman pled guilty for possession with intent to distribute hydrocodone. The woman was an employee of a pharmacy. An accountability audit covering 8 months was conducted and revealed shortages of 10,775 hydrocodone tablets.

[redacted]

A federal grand jury returned an indictment of a medical doctor for enlisting and/or manipulating several individuals into assisting him in filling bogus prescriptions. Using in excess of 18 different pharmacies, the doctor obtained in excess of 1500 dosage units of Percocet and Lortab (hydrocodone) without legitimate medical purposes.

[redacted]

A medical doctor was sentenced for possession of an excess of 15,000 dosage units of hydrocodone.

[redacted]

A medical doctor was convicted of knowingly and intentionally distributing 298 prescriptions for vicodin ES (hydrocodone) without a legitimate medical reason. The prescription contributed to the death of a patient.

[redacted]

A doctor of osteopathy was indicted for using a DEA registration number belonging to another physician (his employer) to obtain Lortab and Tussionex (hydrocodone) for his personal consumption. He allegedly distributed a portion of the controlled substances.

[redacted]

A woman was arrested on 11 counts of obtaining controlled substances. The woman received in excess of 12,000 dosage units of Vicodin (hydrocodone), Darvocet, and Xanax without legitimate prescriptions. Investigators discovered that in a nine month period the woman received approximately 16,000 dosage units of controlled substances with approximately 12,000 of those dosage units not legitimately prescribed or obtained.

[redacted]

A pharmacy technician with a major pharmacy chain was arrested after being videotaped placing tablets from two pharmacy bottles into her purse. The female was found to be in the possession of 100 tabs of hydrocodone and 99 tabs of clorazepate. She admitted to taking the drugs for personal use.

[redacted]

A man was sentenced for the illegal distribution of large quantities of Percocet, Vicodin (hydrocodone), Tylenol #3 and #4, Valium and Xanax.

[redacted]

A registered pharmacist was indicted on five charges of acquiring Lortab (7.5 mg, hydrocodone) by misrepresentation, fraud, forgery, or deception. The individual used the names of area physicians and their DEA registration numbers to forge scripts at the pharmacy where he was employed.

[redacted]

A registered pharmacist was arrested for obtaining Lortabs (7.5 mg, hydrocodone) by fraudulent means and for producing false documents. The individual was using personal computers in his apartment to create and duplicate controlled substance prescriptions.

[redacted]

The owners of a pharmacy settled a case involving the pharmacy filling approximately 43 forged prescriptions accounting for in excess of 16,000 tablets of Vicodin ES (7.5 mg, hydrocodone).

[redacted]

A male was arrested for diverting large quantities of drugs from a pharmacy and two pharmacy technicians confessed to diverting large quantities of a number of drugs, including 17,000 dosage units of hydrocodone.

[redacted]

A dentist was sentenced to five years probation and $750 fine and 160 hours of community service for unlawful prescribing of Lortab 7.5 mg (hydrocodone).

[redacted]

A dentist pled guilty to knowingly and intentionally acquiring possession of a controlled substance (Lortabs) by misrepresentation, fraud, forgery, deception, or subterfuge for his own personal use.

[redacted]

A former male drug warehouse employee was arrested for theft and selling of multiple thousand dosage units of Vicodin (hydrocodone) in factory sealed bottles.

[redacted]

The Seattle Diversion Group seized all controlled substances on hand at a pharmacy. The pharmacist had not renewed his license. Accountability records at the pharmacy and at the hospital pharmacy where he had been previously employed revealed shortages of over 21,000 dosage units of Lortab and Lorcet.

[redacted]

A pharmacist was arrested and charged with one count of illegal possession of a controlled substance. The female pharmacist was diverting hydrocodone from her employer, Walmart Pharmacy.

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Administrative responsibilities for evaluating a substance for control under the CSA are performed for HHS by FDA, with the concurrence of the National Institute on Drug Abuse (Memorandum of Understanding, March 8, 1985, 50 FR 9518-20).

This evaluation discusses the scientific and medical information relative to each of the eight factors, presents findings in the three required areas, and a recommendation regarding scheduling. FDA has evaluated all available abuse potential data on hydrocodone combination products currently scheduled in Schedule III, which was the subject of DEA's request. FDA discussion focuses on the hydrocodone combination products, not on hydrocodone drug substance in Schedule II.

After consideration of the scientific and medical evidence presented under the eight factors discussed above, FDA, with concurrence of NIDA, recommends that the hydrocodone combination products remain controlled in Schedule III of the CSA.

II. BACKGROUND

Currently, hydrocodone/acetaminophen combination products have an important and legitimate role in the treatment of pain, and are approved for management of mild, moderate, and severe pain associated with cancer in adults and children (Guideline for the Management of Cancer Pain in Adults and Children, 2005) and are considered a Step 2 therapeutic option on the World Health Organization (WHO) Analgesic Ladder. This guidance for the treatment of cancer pain states that the use of the hydrocodone combination products is recommended prior to the initiation of therapy with a more potent opioid indicated in the treatment of severe pain (World Health Organization, 1986). Nonsteroidal antiinflammatory drugs (NSAIDs) are considered as the first step in analgesic therapy for chronic pain, to be followed by opioids, alone or in combination, when greater analgesia is needed. The use of single entity opioids (Step 3) such as morphine (Schedule II), oxycodone (Schedule II), hydromorphone (Schedule II), and fentanyl (Schedule II) is indicated when the combination products containing lower doses of opioids have failed.

As described in the hydrocodone/acetaminophen monograph in the Clinical Pharmacology Online database, these products are prescribed for severe cancer pain and other chronic and acute pain. The recently published Opioid Guidelines in the Management of Chronic Non-Cancer Pain (2006) indicates that opioids are effective and extensively used by as many as 90 percent of patients for chronic pain in pain management settings and effective in managing chronic pain.

Other opioid analgesic combination products currently on the market include oxycodone in combination with acetaminophen or aspirin (Schedule II); codeine in combination with acetaminophen or in combination with aspirin, butalbital, and caffeine, or in combination with carisoprodol and aspirin (Schedule III); and, propoxyphene in combination with acetaminophen (Schedule IV).

Hydrocodone combination products are widely prescribed and used in the United States. In 2006, there were approximately 113 million prescriptions for hydrocodone combination products, which correspond to approximately 41 million of patients. In contrast, in 2006, there were approximately 38 million prescriptions for oxycodone-containing products (Schedule II), or approximately 13.7 million patients. In 2006, only about 23 million prescriptions for propoxyphene products and 21 million prescriptions for codeine containing products were issued.

Codeine and acetaminophen combination products (Schedule III) are approved for relief of mild to moderately severe pain. Codeine combined with acetaminophen or aspirin is not as frequently prescribed as the hydrocodone combinations. Codeine requires metabolism by the cytochrome P450 enzyme, 2D6, to its active metabolite, morphine, and as many as 7 percent of the U.S. population lacks adequate 2D6 levels for this metabolic activity (Poolsup *et al*., 2000). Therefore, these products are not effective in this population. In 2006, 21 million prescriptions for codeine containing products were dispensed, compared to 113 million prescriptions for hydrocodone combination products. In 2006, approximately 13 million patients received a prescription for codeine containing products, compared to approximately 15.8 millions of patients in 2002.

Changes in the scheduling of hydrocodone could have a number of effects. First, because prescriptions for Schedule II drugs are required to be handwritten; more doctor visits may be needed to obtain the refills for patients who receive Schedule II products chronically. If patients do not have ready access to a physician each time a refill is needed, they might seek alternative, potentially inappropriate treatments or choose to go without treatment for their pain, leading to adverse health outcomes. The unintended consequences of changes affecting prescribing requirements have been observed at the state level, when in 1989 the State of New York imposed a triplicate program for the widely used benzodiazepine agents. Ross-Degnan *et al*. (2004) and Simoni-Wastila *et al*. (2004) showed that the New York program reduced use of benzodiazepines among chronically ill patients for whom these agents represent effective treatments. These investigators also concluded that the largest reduction in benzodiazepine use was seen among patients with seizure disorders. Furthermore, they concluded that this program did not reduce the problematic use of these drugs.

Changes in the scheduling for hydrocodone combination products could also drive the use of alternative treatments with significant abuse potential. For example, frequency of use of the approved oxycodone products may increase relative to the hydrocodone/acetaminophen combination products if the latter become listed in Schedule II. Finally, rescheduling of hydrocodone combination products could result in a switch to less efficacious pain medications, such as NSAIDs, though they are generally not adequate for treating severe pain, or lead to people leaving their pain untreated, leading to loss of functioning and activity.

III. EVALUATING HYDROCODONE COMBINATION PRODUCTS UNDER THE EIGHT FACTORS

This section presents the current scientific and medical knowledge about hydrocodone combination products.

1. ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

The term "abuse" is not defined in the CSA. When assessing the abuse potential of a substance, the Secretary considers numerous factors, including the prevalence and frequency of use in the general public and in specific subpopulations, the amount of the material that is available for illicit use, the ease with which the substance may be obtained or manufactured, the reputation or status of the substance "on the street," evidence relevant to population groups that may be at particular risk, and relationship to a substance already listed.

Abuse potential is a complex determination with many dimensions. There is no single test or assessment procedure that, by itself, provides a full and complete characterization. Thus, no single measure of abuse potential is ideal. Scientifically, a comprehensive evaluation of the relative abuse potential of a drug substance includes consideration of the drug's receptor binding affinity, preclinical pharmacology, reinforcing effects, discriminative stimulus effects, dependence producing potential, pharmacokinetics and routes of administration, toxicities, assessment of the clinical efficacy-safety database relative to actual abuse, clinical abuse potential studies, and the public health risks following marketing of the substance.

Animal data, human data, and epidemiological data are all used in determining a substance's abuse potential. Epidemiological data can also be an important indicator of actual abuse. Finally, evidence of clandestine production and illicit trafficking of a substance are also important factors.

In considering the request by DEA to consider placing hydrocodone combination products in Schedule II under the CSA, FDA has evaluated all available data on the combination products.

Hydrocodone (dihydrocodeinone) is a semisynthetic opioid derived from codeine. Like morphine and other morphine-like opioid substances, hydrocodone produces analgesia, depresses the cough reflex, reduces gastrointestinal motility, produces respiratory depression, miosis, and has the potential of being abused. Hydrocodone and related opioids produce their major effects in the central nervous system (CNS) through interaction with opioid receptors. There are three well-characterized opioid receptors known as mu (μ), delta (δ) and kappa (κ). Both, hydrocodone and morphine exert their main effects through the interaction with the μ opioid receptor (Gutstein and Akil, 2006). For detailed data on *in vitro*

binding studies and activation of the opioid receptors, see Factor 2 entitled, "SCIENTIFIC EVIDENCE OF THE DRUG'S PHARMACOLOGICAL EFFECT," below.

Hydrocodone substance is considered to have high potential for abuse and has been listed in Schedule II of the CSA since enactment in 1971. However, combination products containing hydrocodone and either an isoquinoline alkaloid of opium or one or more nonnarcotic therapeutically active ingredients were placed in Schedule III of the CSA by Congress, based upon the concentration of hydrocodone and the second component of the combination product. DEA states in its transmittal of the petition it received and its request for a medical and scientific evaluation and scheduling recommendation, that it is generally believed that the addition of isoquinoline alkaloids and other nonnarcotic ingredients reduce the abuse potential of hydrocodone combination products relative to hydrocodone substance.

Several combination products containing hydrocodone in combination with acetaminophen, aspirin, ibuprofen, and homatropine are currently marketed as analgesics for pain relief and as cough suppressants. Currently marketed hydrocodone combination products include analgesics such as Vicodin, Vicoprofen, Lortab, Lorcet, Norco, Co-Gesic, Hydrocet, Anexsia, Azdone, Zydone, and cough suppressants such as Hycodan, Mycodone, Tussionex Pennkinetic,Tussigon and several generics). In 2006, 113 million prescriptions for hydrocodone/acetaminophen were dispensed in the United States [Verispan, Vector One™: National (VONA)][1], representing over 41.1 million of patients [Vector One™: Total Patient Tracker (TPT)][2].

The clinical rationale for the less restrictive schedule for hydrocodone combination products compared to the schedule for hydrocodone substance takes into consideration the potentiation of therapeutic effects of hydrocodone (enhancement of analgesia) by the addition of a nonnarcotic ingredient in a recognized therapeutic amount, thus reducing the amount of hydrocodone needed to achieve the desired therapeutic effect and reducing adverse events. Thus, hydrocodone and the nonnarcotic analgesic ingredient contribute to the enhanced analgesic effect of the combination products (Beaver, 1984). The subjective opioid effects associated with potential for abuse, such as euphoria and liking, as well as the adverse effects produced by hydrocodone are dose-related. By reducing the amount of hydrocodone needed to achieve the desired therapeutic effect, the likelihood of producing positive opioid reinforcing effects is reduced.

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[1] Verispan's Vector One™: National 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. The Vector One™ database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups.

[2] Verispan's Vector One™: Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes. Total patient numbers are determined by unique patient counts projected to a national total of retail prescriptions.

Therefore, hydrocodone combination products have less abuse potential than hydrocodone substance.

Beaver (1984) has demonstrated that combining an optimal dose of acetaminophen or aspirin with hydrocodone or oxycodone produces an additive analgesic effect which is greater than that obtained by doubling the dose of either constituent administered alone. The abuse potential of hydrocodone substance has been studied in animals and in human volunteers. Hydrocodone substance functions as a positive reinforcer in rats in self-administration studies, and in drug discrimination studies substitutes for morphine in both rats and primates (Tomkins *et al.*, 1997; Lelas *et al.*, 1999). Self-administration and drug discrimination studies are typically conducted on substances and not on combinations of substances.

In subjects with a history of opioid abuse, but who were not physically dependent at the time of the studies, (Fraser and Isbell, 1950; Jasinski and Martin, 1967) hydrocodone (Schedule II) produced signs and symptoms that were similar to those of the typical μ opioid agonist morphine (Schedule II), including drug liking and euphoria. However, in non-drug abusing volunteers, oral hydrocodone generated subjective effects indicative of both positive and unpleasant effects (Kaplan *et al.*, 1997).

Zacny (2003) studied the pleasant subjective, psychomotor, and physiological effects of hydrocodone in non-drug abusing volunteers elicited by the recommended therapeutic dose of Hycodan (Schedule III combination product containing hydrocodone and homatropine methylbromide) and at four times the recommended dose. Hycodan tablets and syrup contain hydrocodone (5 mg per tablet or teaspoon) as an antitussive agent, and a subtherapeutic amount of the anticholinergic substance homatropine methylbromide (1.5 mg per tablet or teaspoon) to discourage deliberate overdosage. This non-drug abusing population closely mirrors patients taking hydrocodone combination products for its therapeutic effects. Effects of Hycodan (Schedule III) were compared to the effects of morphine (Schedule II) and lorazepam (Schedule IV) which was used for its performance impairment properties. Hycodan at four times the therapeutic recommended dose had similar effects to morphine, in producing pleasant as well as unpleasant effects (dizziness, drug disliking), while producing a less marked psychomotor cognitive impairment than that observed with lorazepam. Post-session ratings of overall liking were not significant (Zacny, 2003). Therefore, when increasing the dose of the hydrocodone combination cough suppressant product, the drug produces a mixture of pleasant and unpleasant effects, with the unpleasant effects limiting the abuse potential of this combination. The nonnarcotic ingredients of the hydrocodone combination products limit the abuse potential of the products because they elicit toxic, dysphoric, and/or unpleasant effects, which are exacerbated as the doses of the product are increased. Therefore, any desired effects from hydrocodone are mitigated by the unpleasant effects of the other ingredients in the combination. This effect essentially vitiates

and decreases the abuse potential of the product relative to any single entity product of hydrocodone substance. See Factor 3 entitled, "THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCES," below for a description of the unpleasant effects attributed to the nonnarcotic ingredients in the hydrocodone combination products.

In a similar clinical abuse liability study, Zacny and Bolbolan (2005) reported the dose-related opioid effects of hydrocodone/acetaminophen in a population of recreational drug users. At the highest dose tested of 20 mg of hydrocodone and 1,000 mg of acetaminophen, the combination produced similar effects to those of 40 mg of morphine. Were this combination an approved product, it would be listed in Schedule II because the amount of hydrocodone is outside of the specified amount required for a Schedule III product. Some subjects experienced unpleasant adverse events while others had elevated liking ratings. The 5 mg hydrocodone/500 mg acetaminophen dose did not produce significant effects on any of the subjective measures. The 10 mg hydrocodone/500 mg acetaminophen dose produced effects similar to those of morphine, but many of the effects did not significantly differ from placebo.

In conclusion, and as detailed above, the addition of a nonnarcotic active ingredient lowers the potential for abuse of hydrocodone combination products (Schedule III) compared to hydrocodone substance (Schedule II) in two ways:

(1) By reducing the amounts of hydrocodone needed to reach the desired therapeutic effect and limiting in this way the intake of hydrocodone to lower doses that might not be perceived by patients as reinforcing and pleasant; and,

(2) By the mediation of toxic, dysphoric, and unpleasant effects if high doses of these products are ingested for abuse and misuse purposes.

2. SCIENTIFIC EVIDENCE OF THE DRUG'S PHARMACOLOGICAL EFFECT

Hydrocodone is marketed primarily for therapeutic purposes in fixed combinations with nonopiate drugs, such as acetaminophen, aspirin and ibuprofen, chlorpheniramine, and homatropine methylbromide. Combination products of hydrocodone with NSAIDs are indicated for the management of moderate to moderately severe pain, whereas the combination products of hydrocodone with homatropine or chlorpheniramine are used for the relief of cough. The combination products are listed in Schedule III of the CSA.

Pharmacologically, hydrocodone mediates analgesia and acts as cough suppressant through a different mechanism than the other components of the available combination products.

The next subsections describe the mechanism of action of hydrocodone, NSAIDs, the pharmacological basis of the combination hydrocodone/NSAIDs combination products, and the pharmacological basis for the hydrocodone/chlorpheniramine and hydrocodone/homatropine methylbromide combinations.

a. Mechanism of Action of Hydrocodone

Hydrocodone is recognized for its analgesic and antitussive properties. These pharmacological effects are mediated through the activation of opioid receptors in the CNS. Each of the three well characterized types of opioid receptors known as μ, δ, and κ is differentially distributed in the CNS and mediates unique pharmacological responses.

Activation of the μ opioid receptors is associated with analgesia, cough suppression, respiratory depression, miosis, inhibition of gastrointestinal motility, and feelings of well-being (euphoria) (Pasternak, 1993).

The κ opioid receptors also mediate analgesia and cough suppression. However, unlike the μ agonists, κ agonists produce dysphoria and mediate psychotomimetic effects, such as disorientation and depersonalized feelings (Pfeiffer *et al.*, 1986).

The consequences of the activation of the δ opioid receptors in humans are not as well-characterized, though in animals, activation of this receptor is correlated with analgesia and cough suppression (Gallantine and Meert, 2005; Kotzer *et al.*, 2000)

Receptor binding studies on cloned human δ, μ, and κ receptors show that hydrocodone displays higher affinity for μ opioids receptors than for κ and δ receptors.[3] In these studies, hydrocodone binds to μ-opioid receptors labeled with the selective ligand DAMGO with a Ki of 36.4±13.15 nM, showing less affinity for δ receptors labeled with DADLE (Ki 1,021±238) and for κ receptors labeled with U69593 (Ki= 717±177) (Kotzer *et al.*, 2000).

Chen *et al.* (1991) observed that hydrocodone binds to the μ opioid receptors in rat brain homogenates labeled with the selective ligand DAMGO with high affinity (Ki =19.8 nM), but with relatively lower affinity when compared to morphine and hydromorphone (hydrocodone, Ki=19.8 nM vs 1.2 nM for morphine and 0.6 nM for hydromorphone). Under the same experimental conditions, oxycodone and codeine bind to μ opioids receptors with lower affinity than hydrocodone with affinity constants in the order of 47.4 nM and 248 nM, respectively.

[3] In binding studies, the affinity of a drug for a receptor can be measured through the calculation of the equilibrium constant or Ki; the lower the Ki, the higher the affinity of the drug for the receptor.

Thompson *et al*. (2004) showed that hydrocodone substance (Schedule II) and oxycodone substance (Schedule II) were 10-fold more potent than codeine substance (Schedule II) in stimulating μ and δ opioid receptor- mediated G-protein activation using agonist-stimulated [^{35}S]GTPγS binding in cells expressing the cloned human μ receptors and expressing endogenous δ receptors.

In conclusion, receptor binding studies show that hydrocodone substance displays high affinity for μ opioid receptors, suggesting that analgesic and antitussive effects of the drug are mediated through the activation of this receptor type. However, hydrocodone substance also binds to the δ and κ receptors, though with less affinity. It is important to note that drugs that are relatively selective at standard doses at one receptor type will interact with other receptor types when taken at higher doses, thus leading to changes in the pharmacological profile.

As seen above, hydrocodone substance is a Schedule II full μ opioid agonist. The addition of a nonnarcotic clinically active substance at therapeutically relevant doses decreases the abuse potential of hydrocodone substance. The second components make a therapeutic contribution and lower the abuse potential of these products relative to hydrocodone substance. Below is discussion of how these components contribute to the overall relative abuse potential and clinical effectiveness of the combination products (Beaver and McMillan, 1980; Beaver, 1984; Zacny, 2003). In addition, see Factor 3 entitled, "THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCES," below for a description of the unpleasant effects produced by the nonnarcotic ingredients in hydrocodone combination products that exacerbate when taken at toxic dosage levels.

b. Mechanism of Action of NSAIDs[4]

The group of drugs known as NSAIDs are a chemically heterogeneous group of substances, often chemically unrelated (although most of them are organic acids), which nevertheless share certain therapeutic actions and adverse effects. This group now includes drugs such as aspirin, ibuprofen, and acetaminophen among others. Toxicity for these three components of the hydrocodone combination products are described under Factor 3 entitled, "THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCES," below.

[4] The information provided in this subsection has been extracted from Goodman and Gilman's *The Pharmacological Basis of Therapeutics* text book. (Burke, Smyth, and FitzGerald in the Chapter titled Analgesic-Antipyretic Agents; Pharmacotherapy of Gout, in the Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th Edition, McGraw-Hill, 2006).

Most currently available traditional NSAIDs act by inhibiting the prostaglandin G/H synthase enzymes, colloquially known as the cyclooxygenases (cyclooxygenases -1 and cyclooxygenases-2).

The inhibition of cyclooxygenase-2 (COX-2) is thought to mediate, in large part, the antipyretic, analgesic, and antiinflammatory actions of NSAIDs, while the simultaneous inhibition of cyclooxygenase-1 (COX-1) largely but not exclusively accounts for unwanted adverse effects in the gastrointestinal tract.

Traditional NSAIDs, including the subclass of selective COX-2 inhibitors, are antiinflammatory, analgesic, and antipyretic. NSAIDs are a chemically heterogeneous group of compounds, often chemically unrelated which nevertheless share certain therapeutic actions and adverse effects. Aspirin inhibits the COX enzymes but in a manner molecularly distinct from the competitive, reversible, active site inhibitors and is often distinguished from other NSAIDs. Similarly, acetaminophen, which is antipyretic and analgesic but largely devoid of antiinflammatory activity, also is conventionally segregated from the group despite its sharing NSAID activity with other actions relevant to its clinical action in vivo.

NSAIDs usually are classified as mild analgesics. However, consideration of the type of pain, as well as its intensity, is important in the assessment of analgesic efficacy. NSAIDs are particularly effective when inflammation has caused sensitization of pain receptors to normally painless mechanical or chemical stimuli. Pain that accompanies inflammation and tissue injury probably results from local stimulation of pain fibers and enhanced pain sensitivity (hyperalgesia), in part a consequence of increased excitability of central neurons in the spinal cord.

c. Pharmacological basis for hydrocodone-NSAIDs combination products

The rationale for combination analgesic products such as hydrocodone with an NSAID such as acetaminophen includes (Beaver, 1984):

1. Increased effects: additive or synergetic analgesic effects of the combination based on analgesia through different pharmacological mechanisms.

2. Decreased adverse reactions: the additive efficacy permits use of lower doses of the individual components in the combination dosage unit, subsequently reducing the frequency or severity of dose-dependent adverse drug reactions.

3. Increased patient compliance: convenience of the combination product over taking the individual components separately.[5]

Opioids are recognized for their role in the management of pain. The various opioid compounds can be differentiated in terms of potency, pharmacokinetics, and adverse events profile. Hydrocodone has high oral availability and 30 mg of oral hydrocodone are considered to produce approximately the same analgesic effect as 60 mg of morphine (Schedule II) administered orally, the same analgesic effects as 30 mg of oxycodone (Schedule II), and similar analgesic effect as 130 mg of codeine or propoxyphene (Gustein and Akil , 2006). When combined with NSAIDs, 30 mg of hydrocodone substance for analgesia are not needed. The therapeutic dose of hydrocodone is reduced to a range (5 to 15 mg) where the reinforcing effects of opioids are diminished.

When employed as analgesics, NSAIDs usually are effective only against pain of low-to-moderate intensity, such as dental pain from routine procedures.

The data available in the literature that assess the efficacy of the combination in comparison to the individual components of combination products are limited. Only four full factorial designed studies of opioid/acetaminophen combinations were identified; one evaluating hydrocodone/acetaminophen, one evaluating oxycodone/acetaminophen, and two evaluating codeine/acetaminophen. A full factorial designed study of a combination product evaluates the efficacy or safety of the combination product and that of each of the individual components of the combination against placebo. There are a few partial factorial design studies, which compare the combination with acetaminophen alone. Beaver (1984) suggested that the combination of codeine and acetaminophen results in an additive analgesic effect compared to the individual components.

The analgesic superiority of hydrocodone/acetaminophen was studied in postpartum women in a randomized, double-blind, placebo-controlled, full factorial study (Beaver and McMillan, 1980). The patients received a single oral dose of hydrocodone/acetaminophen (10/1,000 mg) combination (n=21), hydrocodone (10 mg) (n=22), acetaminophen (1,000 mg) (n=22), or placebo (n=22) followed by a 6-hour pain assessment. All treatments were statistically superior to placebo and the hydrocodone/acetaminophen combination product was noted to provide better pain relief based on measurement of "half-pain gone" as compared to hydrocodone or acetaminophen alone, but failed based on the assessment of the change in pain intensity from baseline.

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[5] There is currently no FDA-approved single entity hydrocodone drug product in the United States.

Although their maximal efficacy is generally much less than the opioids, NSAIDs lack the unwanted adverse effects of opiates in the CNS, including respiratory depression and the development of physical dependence.

Common adverse events from traditional NSAIDs that complicate therapy are gastrointestinal, cardiovascular, renal and renovascular adverse events, and hepatic injury.

Ibuprofen is thought to be better tolerated than aspirin and has been used in patients with a history of gastrointestinal intolerance to other NSAIDs. Nevertheless, 5 to 15 percent of patients experience gastrointestinal side effects.

Other adverse effects of ibuprofen, although reported less frequently, include thrombocytopenia, rashes, headache, dizziness, blurred vision, and in a few cases toxic amblyopia, fluid retention, and edema. Patients who develop ocular disturbances should discontinue the use of ibuprofen. Ibuprofen can be used occasionally by pregnant women; however, the concerns apply regarding third-trimester effects, including delay of parturition. Excretion into breast milk is thought to be minimal, so use of ibuprofen by women who are breastfeeding is recommended with caution (Burke *et al*., 2006).

Overall, acetaminophen is well tolerated and has a low incidence of gastrointestinal side effects. It is available without a prescription and is used as a common household analgesic. However, acute overdosage can cause severe hepatic damage, and the number of accidental or deliberate poisonings with acetaminophen continues to grow. Chronic use of less than 2 grams (g)/day is not typically associated with hepatic dysfunction.

d. Basis for the combination of hydrocodone with chlorpheniramine and for hydrocodone homatropine methylbromide

Hydrocodone is used in combination either with chlorpheniramine or with homatropine methylbromide for its antitussive properties. Both combination products are indicated for the symptomatic relief of cough.

Chlorpheniramine is an antihistamine drug (H_1 receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents the release of histamine from dilating capillaries. Chlorpheniramine prevents sneezing, itchy or watery eyes, runny nose, and other symptoms of cold or allergy.

Homatropine methylbromide is an anticholinergic drug that is used in combination with hydrocodone at a subtherapeutic dosage to suppress deliberate overdosage.

3. THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCES

The discussion in this section presents additional current scientific knowledge about the hydrocodone combination products controlled in Schedule III of the CSA.

This subsection describes the chemical and toxicological properties of hydrocodone, and the nonnarcotic components present in hydrocodone combination products.

a. Hydrocodone

Hydrocodone, also known as dihydrocodeinone, is a semisynthetic opioid derived from the naturally-occurring opioid alkaloid codeine. Hydrocodone can be synthesized by hydrogenation of codeinone, by oxidation of dihydrocodeine or by catalytic rearrangement of codeine (Merck Index, 2001). Chemically, hydrocodone is the 4, 5-epoxy-3-methoxy-17-methylmorphinan-6-one, CAS [125-29-1], $C_{18}H_{21}NO_3$; molecular weight 299.36. The bitartrate salt, CAS [34195-34-1] is the main active component in all the hydrocodone combination products currently on the market. Hydrocodone bitartrate occurs as fine, white crystals or crystalline powder and is soluble in water and slightly soluble in alcohol (Merck Index, 2001).

The sulfonated styrene-divinylbenzene copolymer complex with hydrocodone, also known as hydrocodone polistirex, is the derivative used in combination with chlorpheniramine polistirex as an antitussive.

The most common adverse effects of hydrocodone substance are lightheadedness, dizziness, sedation, nausea, and vomiting. Other adverse effects include constipation, rash, pruritus, euphoria, and dysphoria. (HSDB - Hazardous Substances Data Bank http://csi.micromedex.com/DATA/HS/HS3097F.htm). As with all opioids, abuse may lead to development of tolerance to some or all of the adverse effects.

b. Acetaminophen

Acetaminophen is also known as 4-hydroxyacetanilide; p-hydroxyacetanilide; p-acetamidophenol; p-acetaminophenol; p-acetylaminophenol; N-acetyl-p-aminophenol; paracetamol. Chemically, acetaminophen is N-(4-hydroxyphenyl) acetamide, CAS [103-90-2], $C_8H_9NO_2$; molecular weight 151.16. Acetaminophen occurs as large monoclinic prisms, crystallizing from water. It is very slightly soluble in cold water, considerably more soluble in hot water, soluble in methanol, ethanol, dimethylformamide, ethylene dichloride, acetone, ethyl acetate, slightly soluble in ether, and practically insoluble in petroleum ether, pentane, and benzene (Merck Index, 2001).

The most common adverse effects of acetaminophen are skin rash and other allergic reactions. Rash is usually erythematous or urticarial but sometimes it is more serious and may be accompanied by drug fever and mucosal lesions. Most serious adverse effect of acute overdosage of acetaminophen is a dose-dependent, potentially fatal hepatic necrosis. Renal tubular necrosis and hypoglycemic coma may also occur. In adults, hepatotoxicity may occur after ingestion of a single dose of 10 to 15 g (140 to 250 mg/kilograms (kg)) of acetaminophen; doses of 20 to 25 g or more is potentially fatal. The hepatotoxicity may precipitate jaundice and coagulation disorders and progress to encephalopathy, coma, and death. Transient azotemia is apparent in most patients, and acute renal failure occurs in some. Hypoglycemia may occur, but glycosuria and impaired glucose tolerance have also been reported. Symptoms during the first 2 days of acute poisoning by acetaminophen do not reflect the potential seriousness of the intoxication. Nausea, vomiting, anorexia, and abdominal pain occur during initial 24 hours and may persist for 1 week or more. Clinical indications of hepatic damage manifest themselves within 2 to 4 days of ingestion of toxic doses. (HSDB, Hazardous Substance Data Bank http://csi.micromedex.com/DATA/HS/HS3001F.htm)

c. Aspirin

Aspirin is also known as salicylic acid acetate; 2-acetoxybenzoic acid; acetylsalicylic acid and 2-(acetyloxy) benzoic acid, CAS [50-78-2], $C_9H_8O_4$, molecular weight 180.16.

Aspirin occurs as needle-like crystals, is odorless, but in moist air it is gradually hydrolyzed into salicylic and acetic acids and acquires the odor of acetic acid, but is stable in dry air. One gram dissolves in 300 milliliter (ml) water at 25°, in 100 ml water at 37°, in 5 ml alcohol, 17 ml chloroform, and 10-15 ml ether. Aspirin is less soluble in anhydrous ether (Merck Index, 2001).

A portion of the U.S. population is allergic to aspirin; susceptible persons can have anaphylactic reactions after ingestion of very small doses, especially in children and asthmatics. The principal primary effects of overdose include: stimulation of the respiratory center; inhibition of citric acid cycle (carbohydrate metabolism); stimulation of lipid metabolism; inhibition of amino acid metabolism; and, uncoupling of oxidative phosphorylation. Respiratory alkalosis, metabolic acidosis, and water and electrolyte loss occur as the principal secondary consequences of salicylate intoxication. CNS toxicity (including tinnitus, hearing-loss, convulsions, and coma), hypoprothrombinemia and noncardiogenic pulmonary edema may also occur. Symptoms of intoxication include: nausea, vomiting, epigastric discomfort, gastrointestinal bleeding (typically with chronic and rarely with acute intoxication); tachypnea and hyperpnea; tinnitus, deafness, sweating,

vasodilatation, hyperpyrexia (rare), dehydration; and, irritability, tremor, blurring of vision, subconjunctival haemorrhages. The following are the effects on blood glucose: hyper- or hypoglycemia; effects on blood: hypoprothrombinemia; effects on liver: increased serum aminotransferase activities (SGOT and SGPT). Noncardiogenic pulmonary edema; confusion, delirium, stupor, asterixis, coma, cerebral edema, acute renal failure; cardio-respiratory arrest occur with severe intoxication only.
(Hazardous Substance Data Bank
http://csi.micromedex.com/DATA/HS/HS652F.htm)

d. Chlorpheniramine

Chlorpheniramine is also known as γ-(4-chlorophenyl)-*N,N*-dimethyl-2-pyridinepropanamine; 2-[*p*-chloro-α-(2-dimethylaminoethyl)benzyl]pyridine; 1-(*p*-chlorophenyl)-1-(2-pyridyl)-3-dimethylaminopropane; 1-(*p*-chlorophenyl)-1-(2-pyridyl)-3-*N,N*-dimethylpropylamine; 3-(*p*-chlorophenyl)-3-(2-pyridyl)-*N,N*-dimethylpropylamine; γ-(4-chlorophenyl)-γ-(2-pyridyl)propyldimethylamine; chlorprophenpyridamine; CAS [132-22-9], $C_{16}H_{19}ClN_2$, molecular weight 274.79 (Merck Index, 2001). The sulfonated styrene-divinylbenzene copolymer complex with chlorpheniramine, also known as chlorpheniramine polistirex, is derivative used in combination with hydrocodone in antitussive formulations.

The most common adverse effects of chlorpheniramine are related to central nervous depression, as evidenced by drowsiness, lethargy, fatigue, hypnosis, and coma. Related nervous symptom effects include vertigo, ataxia, tinnitus, and blurred vision. Central nervous hyperexcitability often follows initial sedation; in children excitement is often first evidence of poisoning. The stimulant phase brings tremors, anxiety, insomnia, excitement, hallucinations, delirium, toxic psychosis, and convulsions. Dangerous hyperpyrexia may occur in poisoned children. Gastrointestinal reactions include dry mouth, anorexia, nausea, vomiting, abdominal distress, constipation, and/or diarrhea.
(Hazardous Substance Data Bank
http://csi.micromedex.com/DATA/HS/HS3032F.htm)

e. Ibuprofen

Ibuprofen is also known as *p*-isobutylhydratropic acid; (±)-2-(4-isobutylphenyl)propionic acid and α-methyl-4-(2-methylpropyl)benzeneacetic acid, CAS [15687-27-1], $C_{13}H_{18}O_2$, molecular weight 206.28. It is a colorless crystalline stable solid, relatively insoluble in water and readily soluble in most organic solvents (Merck Index, 2001).

The most common adverse effects of ibuprofen are related to gastrointestinal side effects: epigastric pain, nausea, heartburn, and sensations of 'fullness' in the gastrointestinal tract are the usual difficulties. Other side effects of

ibuprofen have been reported less frequently. They include thrombocytopenia, skin rashes, headache, dizziness and blurred vision, and in a few cases, toxic amblyopia, fluid retention, and edema. In ibuprofen overdose cases, primarily nausea or vomiting are experienced. (Hazardous Substance Data Bank http://csi.micromedex.com/DATA/HS/HS3099F.htm)

f. Homatropine methylbromide

Homatropine methylbromide is chemically known as 8-azoniabicyclo[3.2.1]octane, 3-[(hydroxyphenylacetyl)oxy]-8,8-dimethyl-, bromide, *endo*-; or as 3α-hydroxy-8-methyl-1αH,5αH-tropanium bromide mandelate, CAS [80-49-9], $C_{16}H_{21}NO_3.CH_3Br$, molecular weight 370.28. It occurs as minute needles, is freely soluble in water and diluted alcohol; slightly soluble in absolute alcohol; and, insoluble in ether (Merck Index, 2001; USP Dictionary of USAN and International Drug Names, 2005). The most common adverse effects of homatropine, atropine, and other antimuscarinics are dose-related and are usually reversible when therapy is discontinued. At therapeutic doses, adverse effects include dryness of the mouth with difficulty in swallowing and talking, thirst, reduced bronchial secretions, dilatation of the pupils (mydriasis) with loss of accommodation (cycloplegia) and photophobia, flushing and dryness of the skin, transient bradycardia followed by tachycardia, with palpitations and arrhythmias, and difficulty in micturition, as well as reduction in the tone and motility of the gastrointestinal tract leading to constipation. Some of the central effects of atropine and other tertiary antimuscarinics seen at toxic doses may also occur at therapeutic doses. In overdosage, the peripheral effects become more pronounced and other symptoms such as hyperthermia, hypertension, increased respiratory rate, and nausea and vomiting may occur. A rash may appear on the face or upper trunk. Toxic doses also cause CNS stimulation marked by restlessness, confusion, excitement, ataxia, incoordination, paranoid and psychotic reactions, hallucinations and delirium, and occasionally seizures. However, in severe intoxication, central stimulation may give way to CNS depression, coma, circulatory and respiratory failure, and death. (Martindale - The Complete Drug Reference - Monographs http://csi.micromedex.com/DKS/DATA/MT/MTM335-j.htm#335-a2-b).

4. Its History and Current Patterns of Abuse

Several population-based epidemiologic data sources are useful for assessing historical and current patterns of abuse of hydrocodone combination products. These databases include the National Survey on Drug Use and Health (NSDUH), the Drug Abuse Warning Network (DAWN), the Monitoring the Future (MTF), the Treatment Episode Data Set (TEDS) and the Florida Medical Examiners Commission Data on Drug-Related Deaths. These databases basically provide abuse and usage information on drug products that are marketed in the United States. Thus, since hydrocodone is only marketed in the United States as

combination drug products, these databases provide information only on those products (in Schedule III) and not on hydrocodone substance (Schedule II).

The codeine combination products are in Schedule III and V and these databases provide information on the combination of different formulations of codeine in different combinations and dosage levels. In the case of oxycodone, which is available in the United States as a single ingredient drug product and as a combination product, the information provided relate to a mixture of single entity and combination products. The propoxyphene dosage units (Schedule IV) are also single entity and combination products.

Analysis of the data for the Schedule III hydrocodone combination drugs from these sources is provided below. For comparative purposes, analysis of the same data sources are applied to opioids that cover the range of CSA control levels from Schedule II to IV. Thus, the following analysis compares abuse indicators for products of hydrocodone (Schedule III) with those for oxycodone (Schedule II), propoxyphene (Schedule IV) and codeine (Schedule III and V).

a. National Survey on Drug Use and Health (NSDUH), formerly the National Household Survey on Drug Abuse (NHSDA), managed by the Substance Abuse and Mental Health Services Administration (SAMHSA)

NSDUH, formerly NHSDA, measures the prevalence and risk and protective factors of drug use in the United States. The survey provides data on drug abuse by the general U.S. population age 12 and older. The NSDUH provides yearly national and state level estimates of alcohol, tobacco, illicit drug, as well as for the nonmedical use prescription drug.[6] The present analysis focuses on the comparison of substance use prevalence estimates by lifetime (i.e., ever used), past year and past year abuse or dependence for 2002-2005, in which 2005 is the most current survey data available.

i. Lifetime nonmedical use

[6] The NHSDA/NSDUH surveys provide annual estimates on the lifetime nonmedical use of pain relievers. Separate measurements on the nonmedical use of hydrocodone began in 1999 and continue to present. The survey, however, does not allow for codeine and propoxyphene to be estimated separately. Thus, the present analysis provides a single estimate that combines the nonmedical use of both codeine and propoxyphene. Because of methodological changes to the survey in 2002, the 2002 data constitute a new baseline for tracking trends in substance use and other measures. In 2002 the name of the survey changed from NHSDA to NSDUH. Each NSDUH respondent completing the interview is given an incentive payment of $30. These changes have been attributed to an improvement in the response rate, and affected respondents' reporting of items that are the basis of prevalence measures produced each year. As a result of the changes in the survey methodology, estimates from the 2002 through 2005 are not comparable to estimates from the 2001 and earlier surveys to assess changes in substance use and mental health problems over time.

"Lifetime prevalence" is a cumulative indicator of the total number of people who have ever tried drugs, including many in the distant past. By definition, lifetime use can't be reversed and is not expected to fall quickly, no matter how many people stop taking drugs or are prevented from initiating the use of drugs. Rather than a decline, lifetime prevalence tends to rise each year, regardless of trends in current use (European Monitoring Centre for Drugs and Addiction, 2002). This sections provides support that lifetime nonmedical use relative to availability (measured as number of prescriptions dispensed annually) of hydrocodone combination products (Schedule III) is less than that of oxycodone (Schedule II) relative to availability.

NSDUH asks respondents age 12 or older questions about their nonmedical use of prescription-type drugs, including prescription pain relievers, during their 1) lifetime; 2) past year use; and, 3) clinical symptoms related to drug abuse and dependence. Respondents are asked the specific question: ***"Have you ever, even once, used (a pain reliever) that was not prescribed for you or that you took only for the experience or feeling it caused?***" If a respondent responds affirmatively, then they are given a pill "show card" with pictures of various analgesics and asked to identify which ones they had taken. National estimates on nonmedical use of hydrocodone combination products were first collected in 1999.

In 2005, an estimated 48 million Americans age 12 or older had used prescription-type psychotherapeutic drugs nonmedically at least once in their lifetime (lifetime use). Of these, 32 million used pain relievers, 21 million used tranquilizers, 10 million used stimulants, and approximately 9 million used sedatives. Each of these estimates is similar to the corresponding estimate for 2004.

The survey shows that there was a significant increase in lifetime nonmedical use of pain relievers between 2002 and 2003 among persons age 12 and older. The proportion of the population over age 12 that reported lifetime use of "any pain reliever" remained relatively constant for 2003-2005. However, when analyzing these numbers it should be considered that "lifetime prevalence" is a cumulative indicator of the total number of people who have ever tried drugs, including many in the distant past.

As presented in **Table 1**, of the 32 million Americans that had used pain relievers as a class nonmedically in their lifetime, more than 18 million individuals in 2005 reported lifetime nonmedical use of hydrocodone combination products (Schedule III), representing 8 percent of the population age 12 years old or older. Lifetime users of oxycodone (Schedule II) accounted for more than 12 million, representing 5 percent of the U.S. population age 12 and older. For products containing either codeine or propoxyphene (Schedule III or V and IV, respectively), more than 19 million individuals reported lifetime nonmedical use in 2005 representing 8 percent of the population.

Table 1: Lifetime Users of Any Pain Relievers and Selected Specific Groups of Pain Relievers among Persons Age 12 or Older: Number (in Thousands) and Percent of U.S. Population 12 years of age and older (in Parenthesis), 2002-2005.

DRUG	2002	2003	2004	2005
Any Pain Reliever[1]	29,611 (12.6)	31,207 (13.1)	31,768 (13.2)	32,692 (13.4)
Hydrocodone combinations[1,2]	13,952 (5.9)	16,808 (7.1)	17,734 (7.4)	18,875 (7.8)
Oxycodone [1,3]	10,151 (4.3)	11,538 (4.9)	11,925 (5.0)	12,029 (4.9)
Propoxyphene or Codeine [1,4]	20,653 (8.8)	21,428 (9.0)	21,066 (8.8)	20,944 (8.6)

[1] Includes other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category.
[2] Includes Vicodin®, Lortab®, or Lorcet®, and hydrocodone.
[3] Includes Percocet®, Percodan® or Tylox®, and OxyContin®.
[4] Includes Darvocet®, Darvon® or Tylenol® with Codeine, codeine, Phenaphen® with Codeine, propoxyphene, and SK-65®.
Source: SAMHSA, Office of Applied Studies, NSDUH.

For 2002-2005, the absolute number of hydrocodone combination products lifetime nonmedical users exceeds the absolute number of lifetime nonmedical users of oxycodone and it is likely it would exceed estimates for lifetime nonmedical users of codeine and propoxyphene, were the estimates for the two drugs obtained separately. However, these numbers are not normalized for drug availability (number of prescriptions dispensed annually). The overall yearly availability of hydrocodone combination products remains approximately three times greater than that of oxycodone, based on number of prescriptions dispensed. Based on the greater availability of hydrocodone relative to the availability of oxycodone, the hydrocodone combination products (Schedule III) normalized numbers are approximately half of those of oxycodone (Schedule II). This finding supports the conclusion that hydrocodone combination products have a lower relative abuse potential than oxycodone, using this indicator.

ii. Past year Nonmedical Use Estimates

The most recent data demonstrates that the estimates of percentage of lifetime nonmedical users of hydrocodone, oxycodone, propoxyphene, and codeine products reporting past year use remains relatively unchanged from 2002 through 2005 (**Table 2**).

The NSDUH reports past year use of pain relievers as a group. According to the European Monitoring Centre for Drugs and Drug Addiction (2002), past

year or past month use are more appropriate indicators of current drug-use in the general population. Nearly 12 million Americans reported using any pain reliever nonmedically in 2005 (**Table 2**). This number represents approximately 36 percent of those Americans 12 years and older who had reported lifetime use of any pain reliever. In 2005, approximately 8.0 million lifetime nonmedical users of hydrocodone combination products, 4.9 million lifetime users of oxycodone, and 7.8 million lifetime users of either codeine or propoxyphene reported continued use of a pain reliever from the previous year, representing 43 percent, 41 percent, and 37 percent of lifetime users, respectively. These estimates indicate that the percentage of lifetime users of hydrocodone, oxycodone, propoxyphene, and codeine reporting past year use of any pain reliever remained stable for the years 2002 through 2005.

Table 2: Past year nonmedical use of any pain relievers among lifetime nonmedical users of hydrocodone, oxycodone and propoxyphene or codeine combination products, age 12 and older, numbers in thousands and percentages (percent of lifetime users in parenthesis), 2002-2005.

ANY PAST YEAR PAIN RELIEVER USE AMONG LIFETIME USERS OF:	NUMBERS IN THOUSANDS (PERCENTAGES)*			
	2002	**2003**	**2004**	**2005**
Any Pain Reliever	10,992 (37.1)	11,671 (37.4)	11,256 (35.4)	11,815 (36.1)
Hydrocodone combinations[1,2]	6,782 (48.6)	7,679 (45.7)	7,768 (43.8)	8,068 (42.7)
Oxycodone [1,3]	4,286 (42.2)	5,020 (43.5)	5,102 (42.8)	4,973 (41.3)
Propoxyphene or Codeine [1,4]	7,678 (37.2)	7,836 (36.6)	7,701 (36.6)	7,800 (37.2)

* Percentages of lifetime nonmedical users of any pain reliever and specific pain relievers among who reported past year use of any pain reliever.

[1] Includes other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category.

[2] Includes Vicodin®, Lortab®, or Lorcet®, and hydrocodone.

[3] Includes Percocet®, Percodan® or Tylox®, and OxyContin®.

[4] Includes Darvocet®, Darvon® or Tylenol® with Codeine, codeine, Phenaphen® with Codeine, propoxyphene, and SK-65®.

Source: SAMHSA, Office of Applied Studies, 2002-2005 NSDUH.

iii. Past Year Initiates

The ratios of past year initiates of nonmedical use of hydrocodone combination products (Schedule III) relative to prescriptions dispensed (2002-2005), is lower than the corresponding ratio for oxycodone (Schedule II), thus demonstrating their lower relative abuse potential (**Table 3**).

Estimates of the number of persons who used prescription pain relievers nonmedically for the first time in the past year, known as "past year initiates," can also be determined by NSDUH data. Overall, these estimates have remained stable from 2002 to 2005, with an estimated 2.3 million persons initiating first time nonmedical use of prescription pain relievers in 2002; 2.4 million in 2003; 2.4 million in 2004; and, 2.2 million in 2005. Among the past year initiates for prescription pain relievers in the past year, the numbers using oxycodone (Schedule II), hydrocodone combination products, (Schedule III) and codeine or propoxyphene products (Schedule III-IV) were relatively stable between 2002 and 2005, with an estimated 1.3 million persons initiating use of hydrocodone, approximately 0.5 million persons initiating use of oxycodone and approximately 800,000 initiating use of codeine or propoxyphene products in 2005 (**Table 3**).

Table 3: Past year nonmedical use of specific pain relievers among past year initiates of any pain reliever, age 12 and older, numbers in thousands, and ratio of past year initiates per hundred thousand prescriptions dispensed (in parenthesis) 2002 – 2005.

NONMEDICAL USE OF SPECIFIC PAIN RELIEVERS FOR THE FIRST TIME IN THE PAST YEAR -*PAST YEAR INITIATES*	**NUMBERS IN THOUSANDS (*INITIATES /100,000 RX*)***			
	2002	**2003**	**2004**	**2005**
Hydrocodone combinations [1,2]	1,349 (*1,542*)	1,403 (*1,519*)	1,352 (*1,381*)	1,314 (*1,243*)
Oxycodone [1,3]	474 (*1,782*)	503 (*1,725*)	608 (*1,947*)	455 (*1,326*)
Propoxyphene or Codeine [1,4]	952 (*1,790*)	1,039 (*2,033*)	1,002 (*2,092*)	855 (*1,842*)

* Number of people who used specific pain relievers nonmedically for the first time in the past year per 100,000 dispensed that year.

[1] Includes other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category.

[2] Includes Vicodin®, Lortab®, or Lorcet®, and hydrocodone.

[3] Includes Percocet®, Percodan® or Tylox®, and OxyContin®.

[4] Includes Darvocet®, Darvon® or Tylenol® with Codeine, codeine, Phenaphen® with Codeine, propoxyphene, and SK-65®.

Source: SAMHSA, Office of Applied Studies, 2002-2005 NSDUH.

In 2002 through 2005, the numbers of people 12 years old or older who initiated nonmedical use of opiates relative to availability are presented in **Table 3**. The analyses relative to drug availability of past year initiates per hundred thousand prescriptions dispensed show that hydrocodone combination products (Schedule III) differentiates from oxycodone (Schedule II) and from codeine or propoxyphene products (Schedule III- IV) with a lower rate of abuse. In conclusion, if these drugs were equally

available, the data indicates that a greater number of people would elect to initiate the use of oxycodone (Schedule II) over hydrocodone combination products (Schedule III), and over codeine or propoxyphene (if the estimates for the two drugs were obtained separately). Using this indicator, this finding supports the conclusion that hydrocodone combination products have a lower relative abuse potential than oxycodone.

iv. Past Year Use and Past Year Abuse or Dependence

The data shows that individuals who used oxycodone (Schedule II) nonmedically in their lifetime develop a substance use disorder (abuse or addiction) at a higher rate than those who used hydrocodone combination products (Schedule III), codeine or propoxyphene (Schedule III-IV) (**Table 4**).

NSDUH includes a series of questions to assess the prevalence of substance use disorders (i.e., dependence on or abuse of a substance) in the past 12 months. These questions are used to classify persons as dependent on or abusing specific substances, based on criteria specified in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association [APA], 1994).

Overall, the number of persons age 12 and older with substance abuse or dependence disorders to pain relievers remained stable from 2002 to 2005, with an estimate of 1.5 million in 2002; 1.4 million in 2003; 1.4 million in 2004; and, 1.5 million in 2005. These numbers represent approximately 0.6 percent of the entire noninstitutionalized U.S. population age 12 and over.

In 2005, among persons who reported lifetime use of hydrocodone combination products, 1.2 million were identified as dependent on or abusing any pain reliever (**Table 4**). In the same year, approximately 1 million persons who reported lifetime use of oxycodone and 1.2 million of those who reported lifetime use of codeine or propoxyphene products met abuse or substance dependence criteria to any pain reliever in the past year. These numbers represent approximately 6 percent of the lifetime users of hydrocodone products, 8 percent of the lifetime oxycodone products users, and 6 percent of the codeine or propoxyphene lifetime users met substance abuse or dependence in the past year. These estimates indicate that those individuals who used oxycodone (Schedule II) nonmedically in their lifetime are more likely to become addicted to opiates than those who used hydrocodone combination products (Schedule III), codeine products (Schedule III-IV), or propoxyphene (Schedule IV). Using this indicator, this finding supports the conclusion that hydrocodone combination products have a lower relative abuse potential than oxycodone.

Table 4: Past year abuse or dependence on any pain relievers among lifetime nonmedical users of hydrocodone combination products (Schedule III), oxycodone (Schedule II), and codeine or propoxyphene (Schedule III-IV) products, age 12 and older, numbers in thousands and percentages in parenthesis, 2002-2005.

ANY PAIN RELIEVER ABUSE OR DEPENDENCE AMONG LIFETIME USERS OF:	NUMBERS IN THOUSANDS (PERCENTAGES)*			
	2002	2003	2004	2005
Hydrocodone [1,2]	1,042 (7.5)	1,061 (6.3)	1,094 (6.2)	1,210 (6.4)
Oxycodone [1,3]	876 (8.6)	915 (7.9)	873 (7.3)	985 (8.2)
Propoxyphene or Codeine [1,4]	1,233 (6.0)	1,161 (5.4)	1,086 (5.2)	1,274 (6.1)

[*] Number of persons in percentages who met DSM-IV criteria for substance abuse or dependence on any pain reliever among lifetime users of specific pain relievers

[1] Includes other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category.

[2] Includes Vicodin®, Lortab®, or Lorcet®, and hydrocodone.

[3] Includes Percocet®, Percodan® or Tylox®, and OxyContin®.

[4] Includes Darvocet®, Darvon® or Tylenol® with Codeine, codeine, Phenaphen® with Codeine, propoxyphene, and SK-65®.

Source: SAMHSA, Office of Applied Studies, 2002-2004 NSDUH.

b. Monitoring the Future (MTF, 2006)

MTF (2006) is an ongoing study sponsored by the National Institute on Drug Abuse (NIDA) conducted at the University of Michigan.[7]

From the first series of questions from the MTF survey, the hydrocodone/acetaminophen combination Vicodin (Schedule III) had an annual prevalence of 4.2 percent in 2006, whereas the Schedule II oxycodone containing products OxyContin, Percocet (oxycodone/acetaminophen) and Percodan (oxycodone/aspirin) each had an annual prevalence of 2.8, 2.2, and 0.3, respectively, and codeine of 3.4. Prevalence refers to the proportion or percentage

[7] Each year MTF surveys a total of approximately 50,000 students in the 8th, 10th, and 12th grades in classrooms during the spring of each year, and it also collects data by mail from a sub-sample of adults who had participated earlier in the study as 12th graders (Johnston et al. 2007). In addition to tracking the use of marijuana, heroin, hallucinogens, amphetamines, methamphetamines, alcohol and cigarettes, the survey asks participants about their use of narcotics other than heroin. The survey only reports on the use of "narcotics other than heroin" for 12th graders and older populations. This class includes specific narcotics such as Vicodin (Schedule III, hydrocodone/acetaminophen combination), OxyContin (Schedule II, oxycodone), Percocet (Schedule II, oxycodone/acetaminophen), Percodan (Schedule II,oxycodone/aspirin), and codeine (Schedule III-IV). Questions regarding OxyContin, Vicodin, Percocet, Percodan, and Dilaudid (hydromorphone, Schedule II) were added in 2002.

of the sample reporting use of a given substance on one or more occasions in a given time interval. Thus, annual prevalence refers to the percentage of the

respondents that reported use of a given substance in the past 12 months (Johnston *et al.*, 2007). These numbers indicate that the rate of misuse of oxycodone products is similar to that of the identified hydrocodone combination product, even though there is a lower amount of oxycodone available for potential misuse or abuse compared to the hydrocodone combination product, based on of a lower number of prescriptions dispensed for oxycodone.[8] The information provided by the MTF database relates to Vicodin (Schedule III), which is only one of the several hydrocodone combination products.

Also in 2002, separate tripwire questions were added to determine the extent of past year use of Vicodin (Schedule III) and OxyContin among 12th graders. A tripwire question asks only about the use of a drug in the last 12 months. On the tripwire questions, the rates for past year use for both drugs are considerably higher among 12 th graders where the comparison is possible. On the tripwire questions for 2006, OxyContin had an annual prevalence rate of 4.3 percent and Vicodin had a rate of 9.7 percent. In 2006, more students reported that they used Vicodin in the past 12 months (9.7 percent) than said they used "any narcotic other than heroin" (9.0 percent), of which it is a subclass. It thus appears that some Vicodin users do not recognize and report it as a narcotic drug.

In summary, in 2006 the annual prevalence of OxyContin was estimated to be 4.3 percent in the tripwire question versus 2.8 percent in the branching question, and that of Vicodin was estimated to be 9.7 percent with the tripwire question versus only 4.2 percent in the branching question. These numbers seems to indicate that although the number of prescriptions dispensed for hydrocodone combination products is three times greater than that of oxycodone, the percentage of 12th grades that had tried hydrocodone combination products in the past year in 2006 is not three times higher, as would be expected if these two drugs had the same potential for abuse. The number of prescriptions dispensed of a given drug is used as a measure of how much substance is available for use.

c. Treatment Episode Data Set (TEDS) 2005[9]

TEDS (2005), which does not show that the number of admissions related to treatment for hydrocodone combination products is on the rise, collects data on admissions to drug addiction treatment facilities. Collection of TEDS data for hydrocodone combination products only began in 2004.

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[8] In the MTF questionnaire form that asks about the larger set of specific narcotics as part of a branching question, a respondent must first indicate that he or she used the general class of drugs (e.g., narcotics other than heroin) in the *prior year* before being branched to the more detailed questions about which specific drugs were used.

[9] TEDS is a program coordinated and managed by SAMHSA. This database includes information on treatment admissions that are routinely collected by States to monitor their individual substance abuse treatment systems. Thus, TEDS includes data primarily from treatment facilities that receive public funds. TEDS include information on demographic variables such as age, gender, race and ethnicity, data on primary.

Narcotic analgesic drugs are reported at two levels of detail: 1) a Minimum Data Set collected by all States, and 2) a Supplemental Data Set collected by some States.

(1) The Minimum Data Set is required reporting for all states and jurisdictions. It includes data on admissions related to narcotic analgesics under the substance problem variable by the response category "Other opiates and synthetics." This group includes codeine, hydrocodone, hydromorphone, meperidine, morphine, opium, oxycodone, pentazocine, propoxyphene, tramadol, and any other drug with morphine-like effects, excluding heroin and the nonprescription use of methadone.

(2) The Supplemental Data Set provides a more detailed listing of the substance problem (primary, secondary, and tertiary) and information on specific narcotic analgesics include such as codeine, hydrocodone, hydromorphone, meperidine, oxycodone, pentazocine, propoxyphene, tramadol, and 'Other opiates and synthetics'. [10]

Hydrocodone combination products and tramadol were recently added to the list in March 2004 at the request of the DEA. The other drugs were included in the listing from the beginning of data collection.

TEDS includes data primarily from treatment facilities that receive public funds, and TEDS admissions do not represent individuals. Thus for example, an individual admitted to treatment twice in a calendar year would be counted as two admissions. Also, TEDS reports on the top three drugs of abuse at time of admission. TEDS does not include all drugs that may have been abused prior to admission.

In 2005, there were about 120,000 admissions to treatment where the primary, secondary, or tertiary substance of abuse was an opiate analgesic. For half of these admissions, narcotic analgesics were the primary substance of abuse. The other half represented dual addictions, such as abuse of opiate analgesics in addition to abuse of another substance, such as alcohol or heroin.

The number of treatment admissions in which opiate analgesics were involved has been relatively stable between 1995 and 1997, but increased sharply since 1998 to the present time, with a dramatic increase observed in 2001. The beginning of the sharp rise followed the approval of OxyContin.

[10] States and jurisdictions can choose whether or not to report the detailed listing. Historically, most have not, perhaps because the vast majority of admissions (95percent+ annually) have been for primary use of alcohol, cocaine, heroin, marijuana, and methamphetamine/amphetamine. The number of states reporting detailed drug codes has increased slowly. However, some states, during review and redesign of data collection, have stopped reporting it (e.g., Alabama reported it through 1997, but then stopped). Thus, admission data related to specific drugs is limited.

Rates of narcotic analgesic admission (primary, secondary, or tertiary) per 100,000 population age 12 are particular high in the New England States ranging from 41 per 1000,000 in New Hampshire to 347 per 100,000 in Maine. In 2005, only 11 states collected data on specific opiate analgesics in treatment admissions and only 3 states (Florida, Maryland, and North Dakota) reported admissions involving hydrocodone. In 2005, for these 3 reporting states there were 689 admissions where hydrocodone was a primary, secondary, or tertiary drug, and 2,268 for oxycodone (primary, secondary, or tertiary).

This finding of lower reported admissions for hydrocodone combination products compared to oxycodone (Schedule II), supports the conclusion that hydrocodone combination products have a lower relative abuse potential than oxycodone.

d. Drug Abuse Warning Network (DAWN)

DAWN is a public health surveillance system that monitors drug-related visits to hospital emergency departments (ED) and drug-related deaths reported to DAWN by participating medical examiners and coroners to track the impact of drug use, misuse, and abuse in the United States. As with the NSDUH, SAMHSA is the agency responsible for DAWN operations.

Major changes to DAWN were instituted at the beginning of 2003. These changes are the result of a redesign that, among other improvements, altered most of DAWN's core features, including the design of the hospital sample and the cases eligible for DAWN. These improvements create a permanent disruption in trends. As a result, comparisons cannot be made between old DAWN (2002 and prior years) and the new DAWN systems. Furthermore, changes in the methodology do not allow for national estimates to be computed for 2003, which was the transition year between the two DAWN systems.

SAMHSA is currently working on the calculations of the national estimates for 2004 and 2005 from DAWN. These estimates involve the 2004 and 2005 DAWN data; the medical examiner (ME) data are not affected. Until these 2004 and 2005 estimates are finalized, the most recent DAWN data available to assess national estimates of abuse as indicated by hospital ED's are the 2002 statistics.

i. DAWN- ED Component

Oxycodone (Schedule II) was associated with a higher number of ED mentions than hydrocodone combination products (Schedule III) relative to the number of dispensed prescriptions. Characterizing the scope of abuse in terms of absolute number of cases is misleading in that some opioids are far more available for potential abuse than others. Thus, obtaining a measurement of the relative frequency, or rate of occurrence, of abuse by dividing the numbers of cases that occurred (numerator) by availability, expressed as number of dispensed prescriptions (denominator) and which represents the number of

cases that could have occurred, is more meaningful. Overall, narcotic analgesic ED mentions rose 120 percent from 1997 to 2002.[11] The number of ED mentions during that same period for hydrocodone (Schedule III) rose 118 percent. For oxycodone (Schedule II); ED mentions rose at a more rapid pace (219 percent) and for codeine (Schedule III and V) and propoxyphene (Schedule IV) declined, 37 percent and 28 percent, respectively.

Although absolute number of ED visits increased for hydrocodone and oxycodone from 1994 to 2002 and decreased for codeine and propoxyphene, it is important to note the changes in prescription sales for each drug product as well. In order to accommodate the differences in availability of the product, estimates for rates of ED mentions per prescriptions sold were computed. ED mentions for hydrocodone increased from 18 per 100,000 prescriptions sold in 1997 to 24 per 100,000 prescriptions sold in 2002. The rate for ED visits for oxycodone increased at a steeper rate and ranged from 35 in 1997 to 76 in 2002 per 100,000 prescriptions sold. The rate for ED mentions for codeine decreased from 19 in 1997 to 14 in 2002 per 100,000 prescriptions. The rate for ED mentions for propoxyphene decreased from 21 in 1997 to 16 in 2002 per 100,000 prescriptions sold.

In conclusion, the number of ED mentions of hydrocodone (Schedule III) per 100,000 prescriptions sold increased at a much lower rate than oxycodone (Schedule II).

ii. DAWN- ME Data- pre and post 2002 Data

The number of drug related deaths reported in DAWN is not included for analysis because of the following limitations of the database: DAWN ME data are not a national estimate and cannot be trended. Therefore, it is not possible to compare changes by year of the rate of drug-related deaths per number of prescriptions dispensed for any given drug.

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[11] Prior to 2003, DAWN captured the nonmedical use of a substance either for psychological effects, dependence, or suicide attempt. ED data originate from a representative sample of hospital ED's which are weighted to produce national estimates. According to DAWN methodology, "the terms 'ED drug abuse episode' or 'ED episode' refer to any ED visit that was induced by or related to drug abuse. Similarly, the terms 'ED drug mention' or 'ED mention' refer to a substance that was mentioned in a drug abuse episode. Up to four substances could be reported for each ED episode. Thus, the number of ED drug mentions always equal or exceed the number of ED episodes."

Many factors influence the estimates of ED visits, including trends in the ED usage in general. Some drug users may have visited EDs for a variety of reasons, some of which may have been life threatening events, whereas others may have sought care at the ED for detoxification, because individuals were in need of certification prior to entering treatment. The variable "Motive" applies to the entire episode and since more than one drug can be mentioned per episode, it may not apply to the specific drug for which the tables were created. DAWN data do not distinguish the drug responsible for the ED visit from others used concomitantly.

iii. Florida ME Commission Data on Drug-Related Deaths

In Florida, in 2005 oxycodone was associated with 21 deaths per 100,000 prescriptions, hydrocodone with 8 deaths per 100,000 prescriptions and propoxyphene with 14 deaths per 100,000 prescriptions. At an equal availability of 100,000 prescriptions in the State of Florida, oxycodone (Schedule II) is associated with higher levels of mortality than hydrocodone combination products (Schedule III) and propoxyphene (Schedule IV). These data demonstrate a lower potential for abuse for hydrocodone combination products compared to oxycodone. These data might also reflect a difference in terms of potency, safety, and toxicity between hydrocodone and oxycodone.

The State of Florida prepares an annual report on drug-related deaths using data from toxicology reports submitted to the state Medical Examiners Commission (MEC Drug Report, 2006). This report produces counts of all drug related deaths that are examined by Florida MEs statewide and specifies which of a selected group of drugs of abuse were found in the body of the deceased, and whether that drug was determined to be the cause of death or was merely present at the time of death.

In 2006, Florida reported 731 hydrocodone related deaths, 923 oxycodone related deaths, 328 propoxyphene related deaths, and 318 deaths related to "other opioid." These numbers represent an increase in 2006 of the number of oxycodone related deaths (156 more than 2005); an increase for hydrocodone related deaths (15 more than 2005); and, a decrease in the number of propoxyphene related deaths. Codeine is not reported separately, but in 2006 continues to be the predominant "Other Opioid" reported. For the period 2004 to 2006, oxycodone was associated with 2313 deaths, hydrocodone with 2011, and propoxyphene with 1043 deaths. Taking into consideration availability of these drugs, in the State of Florida in 2005 and 2006, and calculating the number of drug related deaths per 100,000 prescriptions dispensed in the State of Florida, oxycodone (Schedule II) is associated with higher levels of mortality than hydrocodone (Schedule III) and propoxyphene (Schedule IV). This finding supports the conclusion that hydrocodone is associated with lower levels of deaths than oxycodone. This difference might be due to one or a combination of factors, including differences in the potential for abuse, potency, safety, and toxicity.

5. THE SCOPE, DURATION AND SIGNIFICANCE OF ABUSE

The scope of abuse of hydrocodone combination products is comparable to that of other Schedule III opioids.

The 2005 NSDUH indicates that the proportion of the population over age 12 that reported lifetime use of "any pain reliever" remained relatively constant for 2003-2005. In 2005, the lifetime nonmedical use relative to availability of hydrocodone combination products (Schedule III) is less than that of oxycodone (Schedule II) relative to availability. The NSDUH 2005 data also demonstrate that the estimates of percentage of lifetime nonmedical users of hydrocodone, oxycodone, propoxyphene, and codeine reporting past year use of any pain reliever remain relatively unchanged from 2002 through 2005, as well as the number of people initiating the use of any pain reliever among the lifetime users of these drugs. Data on the number of lifetime users of oxycodone or hydrocodone who had developed either abuse or addiction to pain relievers in the past year indicates that those who had used oxycodone in their lifetime are more likely to become addicted to opiates than those who used hydrocodone (Schedule III), codeine (Schedule III-V) or propoxyphene (Schedule IV).

TEDS (2005) does not support the contention that the number of admissions related to treatment for hydrocodone combination products increased from 2004 to 2005. Collection of TEDS data for hydrocodone only began in 2004 and there is no data from TEDS to substantiate that hydrocodone is a primary or even secondary drug of abuse. However, TEDS indicates that overall the number of treatment admissions in which opiate analgesics were involved has increased since 2001, when a sharp increase was observed, to account for 120,000 admissions representing 3.5 percent of the total number of admissions.

The 2006 Florida Medical Examiner's Report shows a higher number of oxycodone related deaths in the State of Florida is greater than the number of deaths associated with hydrocodone.

In addition, in 2004, when DEA requested a medical and scientific evaluation of hydrocodone combination products, it transmitted the following to HHS relative to the hydrocodone combination products and their abuse:

1. DEA stated that hydrocodone is "extensively diverted and abused," but cited data sources fail to present systematically acquired data or cite frequencies of abuse and diversion and compare such calculations to other opiates in different schedules over an extended period of time.

2. DEA stated that abuse of hydrocodone was associated with "considerable morbidity/mortality," but the reports cited to support this do not demonstrate causality attributed to hydrocodone.

3. DEA stated that there is no international diversion issue for hydrocodone, except for possible illegal internet purchases which applies to all controlled substances in any schedules.

4. DEA statement that there is no clandestine production of the hydrocodone combination drugs.

5. As one of the most medically important drugs for treatment of pain, hydrocodone is one of the most prescribed pharmaceutical opiates in United States. DEA stated that production and prescribing of the hydrocodone combination products have increased dramatically in recent years. In March 2004, 116 active dosage form manufacturers registered with DEA.

6. WHAT, IF ANY, RISK THERE IS TO THE PUBLIC HEALTH

This section discusses the adverse events associated with the use of hydrocodone products reported to the FDA.

Adverse events reported by individuals using hydrocodone products to the FDA.

When used as prescribed, the adverse events associated with the use of hydrocodone combination products (Schedule III) are more similar to those of the codeine combination products in Schedules III and V. Based on the Adverse Event Reporting System (AERS) database, the primary risks of the hydrocodone combination products (in Schedule III) and codeine combination products (in Schedule III and V) follow a similar order: 1) overdose (unintentional or intentional), 2) followed by suicide, and then 3) abuse/dependence. Similarly, propoxyphene drug products (Schedule IV) adverse events more likely relate to 1) drug overdose, 2) followed by abuse/dependence, and then 3) suicide. In contrast, most adverse events for the Schedule II oxycodone are associated with 1) abuse/dependence, followed by 2) drug overdose, and then 3) suicide. (See **Table 6**)

As of October 17, 2005, a total of 5,867 serious and nonserious adverse event reports for all hydrocodone products in the FDA's AERS[12], of which 5,740 were domestic reports. These numbers are crude report counts and may include duplicates. These reports were not individually reviewed to determine an association between the reported event and the use of hydrocodone, and it may contain concomitant use of other medications and/or multiple opioid products.

[12] AERS is a computerized information database designed to support FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The ultimate goal of AERS is to improve the public health by providing the best available tools for storing and analyzing safety reports. FDA receives adverse drug reaction reports from manufacturers as required by regulation. Health care professionals and consumers send reports voluntarily through the MedWatch program. These reports become part of an Oracle™ database. The structure of this database is in compliance with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonization. The guidance describes the content and format for the electronic submission of reports from manufacturers. All reported adverse event terms are coded using a standardized international terminology, MedDRA (the Medical Dictionary for Regulatory Activities).

Hydrocodone with acetaminophen was the most commonly reported combination accounting for 3,956 cases.

The top 20 most frequently reported adverse event terms associated with all hydrocodone reports (a report may contain more that one adverse event) received from 1969 to 2005 in the FDA's AERS database, in decreasing frequency, were: Completed Suicide, Multiple Drug Overdose, Overdose, Drug Ineffective, Accidental Overdose, Vomiting, Nausea, Intentional Overdose, Drug Abuser, Coma, Drug Toxicity, Pain, Cerebrovascular Accident, Drug Dependence, Medication Error, Cardio-Respiratory Arrest, Chest Pain, Drug Level Increased, Pruritus, and Myocardial Infarction.

Table 6 shows the numbers of AERS crude reports of overdose, suicides, abuse, dependence, for hydrocodone combination products (Schedule III), oxycodone (Schedule II), codeine products (Schedule III and V), and propoxyphene (Schedule IV) as crude counts and as the percentage that those reports represent from the total number of crude reports for received for each drug.[13] **Table 6** shows that oxycodone was associated with the largest number of overdose, suicide, and abuse and dependence reports, followed by hydrocodone, propoxyphene, and codeine; though caution should be exercised when comparing drug safety issues because of the limitations of the database. [14]

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[13] The MedDRA search terms for Overdose, Suicide and Abuse & Dependence included: Overdoses including intentional overdose (PT), cinchonism (PT), overdose (PT), accidental overdose (PT), multiple drug overdose (PT), multiple drug overdose accidental (PT), and multiple drug overdose intentional (PT)

Suicidal and self-injurious behavior (HLT) including completed suicide (PT), intentional self-injury(PT), suicidal ideation (PT), suicide attempt (PT), self-injurious ideation (PT), self-injurious behavior(PT), and self-mutilation (PT)

Abuse & Dependence terms include chemical and drug abuse (HLT), drug dependence (PT), drug
withdrawal syndrome (PT), drug withdrawal convulsion (PT), drug withdrawal headache (PT), drug withdrawal syndrome neonatal (PT), withdrawal arrhythmia (PT), polysubstance abuse (PT), polysubstance dependence (PT), drug tolerance (PT), drug tolerance increased (PT), dependence(PT), and intentional misuse (PT)

PT - Preferred Term; HLT - High Level Term

[14] AERS accumulated case reports cannot be used to calculate incidence rates or exact estimates of drug risk for a particular product, as reporting of adverse events is a voluntary process, and underreporting exists. Other factors that influence reporting are length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions. It also should be noted that in some of these cases, the reported clinical data were incomplete, and there is no certainty that these drugs caused the reported reactions. These data were generated using computer printouts, and some of the numbers may reflect duplicates.

Table 6: Comparison of crude AERS report counts for drug products containing hydrocodone, oxycodone, codeine and propoxyphene, received since 1969 to 2005.

DRUG	Adverse Event Reports	Overdose Reports (percent Overdose reports/Adverse Event reports)	Suicide Reports (percent Suicide reports/Adverse Event reports)	Abuse and Dependence Reports (percent Abuse and Dependence/Adverse Event reports)
OXYCODONE	15,941	4,531 (28.4)	982(6.2)	5,540 (34.7)
HYDROCODONE	5,867	1,635 (27.9)	791 (13.5)	735 (12.5)
CODEINE	4,262	698 (16.4)	356 (8.4)	241 (5.7)
PROPOXYPHENE	5,270	1,275 (24.2)	437 (8.3)	499 (9.47)

In conclusion, the adverse event profile reported for hydrocodone combination products is different from that reported for oxycodone, with a lower ranking for abuse/dependence, supporting the Schedule III for hydrocodone combination products.

7. ITS PSYCHIC OR PHYSIOLOGICAL DEPENDENCE

Physical dependence is a form of physiologic adaptation to the continuous presence of certain drugs in the body. *Physical dependence* is characterized by the appearance of a withdrawal syndrome when the drug effect significantly diminishes or stops. Opioid withdrawal syndrome can be severe, moderate, or limited and is characterized by autonomic signs such as diarrhea, rhinorrhea, and piloerection, as well as central neurologic arousal with sleeplessness, irritability, and psychomotor agitation (Savage, 2003). The term *psychic dependence* is not in current use and was introduced in the late 1950's by the WHO Expert Committee on Addiction-Producing Drugs, as one of the factors that in conjunction with physical dependence defined the addiction phenomena (Savage *et al.*, 2003).]

Substance dependence as currently defined by the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV) refers to *addiction* rather than to *physical dependence*. The DSM-IV presents seven criteria for *opioid dependence* (DSM-IV-TR, 2000), two of which relate to expected physiological adaptation to opioid use (*physical dependence* and *withdrawal*), and five of which are functional in nature. Three of seven criteria must be met in the context of "a maladaptive pattern of substance use, leading to clinically significant impairment or distress" in order to make a diagnosis of *substance dependence*.

There are several sources of information regarding the development of psychic or physiological dependence by individuals using hydrocodone combination products. These have been discussed previously, and the current section will focus on those aspects of the data that are relevant to psychic or physiological dependence. The first source of data is TEDS, which collects data on admissions to public treatment facilities for drug addiction. TEDS reports on the top three drugs of abuse at time of admission. In 2005, there were about 120,000 admissions to treatment where the primary, secondary, or tertiary substance of abuse was an opiate analgesic. For half of these admissions, narcotic analgesics were the primary substance of abuse. The other half represented dual addictions, such as abuse of opiate analgesics in addition to abuse of another substance, such as alcohol or heroin.

TEDS 2005 shows that there are scant data demonstrating treatment of hydrocodone [whether substance (Schedule II) or combination product (in Schedule III)] dependency as a primary, secondary, or tertiary drug of abuse in treatment clinics. The TEDS data set does not distinguish between admissions involving hydrocodone substance or the combination products. Although hydrocodone combination products have a potential for addiction, TEDS 2005 do not demonstrate that addiction potential of these products is of the same degree as that of other Schedule II opiates, fentanyl, hydromorphone, and oxycodone. Similarly, NSDUH 2005, which measures the prevalence, risks, and protective factors for drug risk, indicates that individuals who used oxycodone (Schedule II) nonmedically in their lifetime develop a substance use disorder (*abuse* or *addiction*) at a higher rate than those who used hydrocodone combination products (Schedule III), codeine (Schedule III and V) or propoxyphene (Schedule IV).

Finally, rates of narcotic analgesic admission (primary, secondary, or tertiary) per 100,000 population age 12 are particular high in the New England States ranging from 41 per 1000, 000 in New Hampshire to 347 per 100,000 in Maine. In 2005, only 11 states collected data on specific opiate analgesics in treatment admissions and only 3 states (Florida, Maryland, and North Dakota) reported admissions involving hydrocodone. In 2005, for these 3 reporting states there were 689 admissions where hydrocodone was a primary, secondary, or tertiary drug, 2,268 for oxycodone (primary, secondary, or tertiary), and 39 admissions for propoxyphene (primary, secondary, or tertiary).

In conclusion, it is expected that patients using hydrocodone products therapeutically for the management of chronic pain, depending on the length of exposure and dose taken, may develop moderate or low *physical dependence*, but not *addiction* which implies impaired control over drug use, compulsive use of the drug despite harm, and craving (that is psychic dependence). Hydrocodone is marketed in the United States only as combination products (Schedule III). Since they are formulated in combination with other drugs, the presence of the two

components of the hydrocodone combination drug product produces an additive analgesic effect that results in a lower dosage of opiate that is needed for pain relief, and thus less frequent occurrence of addiction.

8. WHETHER THE SUBSTANCE IS AN IMMEDIATE PRECURSOR OF A SUBSTANCE ALREADY CONTROLLED UNDER THIS TITLE

Hydrocodone combination products are not immediate precursors of any substance controlled under the CSA, as defined in 21 USC 811(e).

IV. FINDINGS AND RECOMMENDATION

After consideration of the scientific and medical evidence presented under the eight factors discussed above, FDA finds that hydrocodone drug combination products meet the three criteria for placement in Schedule III of the CSA, under 21 U.S.C. 812(b), as distinct from hydrocodone substance in Schedule II.

(A) The drug or other substance has a potential for abuse less than the drugs or other substances in Schedule II.

Hydrocodone substance is a Schedule II full μ opioid agonist. As shown by Beaver and McMillan (1980), Beaver (1984), Zacny (2003), and Zacny *et al.* (2005), the addition of nonnarcotic active ingredients at appropriate doses decreases the abuse potential of the hydrocodone ingredient in the hydrocodone combinations products. The addition of a nonnarcotic active ingredient lowers the potential for abuse of hydrocodone combination products (Schedule III) compared to hydrocodone substance (Schedule II) in two ways. First, the addition of a nonnarcotic active component reduces the amounts of hydrocodone needed to reach the desired therapeutic effect and limits in this way the intake of hydrocodone to lower doses that might not be perceived by patients as reinforcing and pleasant. Second, the nonnarcotic active component cause toxic, dysphoric and unpleasant effects when high doses of these products are ingested for abuse and misuse purposes, and these effects mitigate any desired effects.

Data from population based epidemiological sources such as the NSDUH, 2005; TEDS, 2005; and the Florida Medical Examiners Commission Data on Drug-Related Deaths, 2006, indicate that all hydrocodone products in Schedule III have a lower potential for abuse relative to oxycodone (Schedule II).

The NSDUH 2005 indicates that the lifetime nonmedical use relative to the drug's availability (that is, the number of prescriptions dispensed annually) of hydrocodone (Schedule III) is less than that of oxycodone (Schedule II).

The Florida Medical Examiners Commission Data on Drug-Related Deaths shows that for the period 2004 to 2006, hydrocodone products (Schedule III) were associated with a lower number of deaths than oxycodone (Schedule II). In addition, the number of hydrocodone related deaths relative to availability in the State of Florida is considerably lower than the oxycodone (Schedule II) related deaths relative to their availability.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

Several combination products containing hydrocodone in combination with acetaminophen, aspirin, ibuprofen, and homatropine are currently approved by FDA for use as analgesics for pain relief and as cough suppressants.

(C) Abuse of the drug or other substance may lead to moderate or low physical dependence or psychological dependence and such dependence would be less than the drugs or other substances in Schedule II.

Hydrocodone substance (Schedule II), like all μ opioid agonists, has the potential for producing psychological or physical dependence.

It is expected that patients using hydrocodone combination products (Schedule III) therapeutically for the management of chronic pain, depending on the length of exposure and dose taken, may develop moderate or low *physical dependence*, but not addiction, which implies impaired control over drug use, compulsive use of the drug despite harm and craving.

TEDS 2005 shows that there are scant data demonstrating treatment of hydrocodone [whether substance, (Schedule II) or combination product (in Schedule III)] dependency as a primary, secondary, or tertiary drug of abuse in treatment clinics. TEDS does not distinguish between admissions involving hydrocodone substance or hydrocodone combination products. Although hydrocodone has a potential for addiction, the TEDS 2005 do not demonstrate that addiction potential of hydrocodone is of the same degree as that of other Schedule II opioids, fentanyl, hydromorphone, and oxycodone.

NSDUH 2005 indicates that individuals who used oxycodone (Schedule II) nonmedically in their lifetime develop a substance use disorder (*abuse* or *addiction*) at a higher rate than those who used hydrocodone combination products (Schedule III), codeine (Schedule III), or propoxyphene (Schedule IV).

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FEB 13 2009

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Woodcock:

In accordance with the Controlled Substances Act (CSA) (21 U.S.C. 811(b)), on July 28, 2004, the Drug Enforcement Administration (DEA) forwarded information on the abuse and diversion of hydrocodone combination products to the Department and Health and Human Services (DHHS) for a scientific and medical evaluation and scheduling recommendation. On March 6, 2008, the Assistant Secretary for Health, DHHS, forwarded to the Deputy Administrator of DEA its scientific and medical evaluation entitled, "Basis for the Recommendation to Maintain Hydrocodone Combination Products in schedule III of the Controlled Substances Act" and a letter recommending that hydrocodone combination products continue to be subject to control under schedule III of the CSA.

DEA has continued to monitor the devastating effect that the abuse, trafficking and diversion of hydrocodone has had on the public's health. DEA has collected new data and reanalyzed the existing data regarding hydrocodone. Consequently, DEA believes that this additional data (described in detail in the enclosed document) demonstrates how schedule III controls are not adequate. The magnitude of diversion and abuse is documented in this revised analysis.

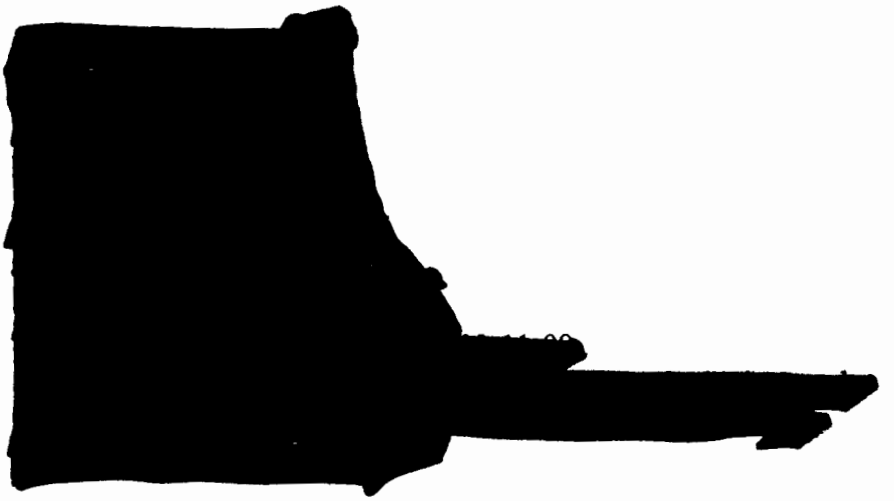
In light of this new data and revised analysis, DEA seeks a re-evaluation of the data and requests a scientific and medical evaluation and scheduling recommendation from DHHS based on these new data.

Should you need any clarification regarding this request, please do not hesitate to contact myself or Dr. Christine Sannerud, Chief, Drug and Chemical Evaluation Section, at (202) 307-7183.

Sincerely,

Joseph T. Rannazzisi
Deputy Assistant Administrator
Deputy Chief of Operations
Office of Diversion Control

Enclosures



Hydrocodone Combination Products:

An Eight-Factor Analysis

February 2009

Prepared by:

Drug and Chemical Evaluation Section
Office of Diversion Control
Drug Enforcement Administration
Washington, D.C. 20537
(202) 307-7183

CHAPTER 1 BACKGROUND

In January 1999, [redacted] a practicing physician specializing in addiction medicine, submitted a petition to the Drug Enforcement Administration (DEA) requesting that proceedings be initiated to reschedule hydrocodone combination products (products containing specified doses of hydrocodone in combination with other drugs in specified amounts) from schedule III to schedule II of the Controlled Substances Act (CSA). The petition contends that evidence of abuse potential is sufficient for these products (henceforth called hydrocodone combination products) to be controlled in schedule II of the CSA.

Upon formal acceptance of the petition by the DEA, in accordance with the CSA (21 U.S.C. 811(b)), DEA gathered the necessary data and on July 28, 2004, forwarded that information to the Department and Health and Human Services (DHHS) for a scientific and medical evaluation and scheduling recommendation. On March 6, 2008, the Assistant Secretary for Health, DHHS, forwarded to the Deputy Administrator of DEA its scientific and medical evaluation entitled, "Basis for the Recommendation to Maintain Hydrocodone Combination Products in schedule III of the Controlled Substances Act" and a letter recommending that hydrocodone combination products continue to be subject to control under schedule III of the CSA. Administrative responsibilities for evaluating a substance for control under the CSA are performed for DHHS by the Food and Drug Administration (FDA), with the concurrence of National Institute on Drug Abuse (NIDA) (in accordance with the Memorandum of Understanding of March 8, 1985, 50F FR 9518-20). The DHHS scientific and medical evaluation document (henceforth called DHHS review document) contained a review of the eight-factors which the CSA requires the Secretary to consider (21 U.S.C. § 811(c)). The factors considered by the Assistant Secretary of Health in preparing the above review with respect to hydrocodone combination products were the following:

(1) Its actual or relative potential for abuse;
(2) Scientific evidence of its pharmacological effects, 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, risks are there to the public health;
(7) Its psychic or physiological dependence liability; and
(8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter. (21 U.S.C. § 811(c)).

The CSA requires DEA to determine whether the DHHS scientific and medical evaluation and scheduling recommendation and "other relevant data" constitute substantial evidence that the drug should be rescheduled as proposed in the petition. This document contains an explanation of the "other relevant data" that DEA considered and it is organized according to the eight factors specified in 21 U.S.C. 811(c). Because "other relevant data" as presented in this document contains substantial amount of new information, DEA, in accordance with the CSA (21 U.S.C. 811(b), is requesting DHHS to reevaluate this petition.

CHAPTER 2 EVALUATING HYDROCODONE COMBINATION PRODUCTS UNDER THE EIGHT FACTORS

1. ITS ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

The CSA defines hydrocodone substance as schedule II, while its products containing specified doses in combination with specified amounts of isoquinoline alkaloid of opium or one or more nonnarcotic substances in recognized therapeutic amounts as schedule III products. The CSA defines schedule III hydrocodone preparations (henceforth called hydrocodone combination products) as the following (21 CFR §1308.13 (d)):

I. 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
II. 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

This differential placement of hydrocodone substance versus its combination products in the CSA suggests that Congress viewed these combination products as having less abuse potential. It is reasonable to assume that Congress believed that the presence of nonnarcotic ingredients in these products reduced their abuse potential. However, the Drug Enforcement Administration (DEA) could not identify any legislative history in support of this supposition. In addition, despite data that identified hydrocodone as a drug with significant analgesic efficacy, most hydrocodone combination products marketed in the U.S. at the time the CSA was enacted were primarily used as antitussive (anti-cough) agents and were less commonly prescribed than other antitussive drugs such as codeine. It is likely that both the limited use and the presumption of reduced abuse liability of hydrocodone products played a role in placing these products in schedule III.

The term "abuse" is not defined in the CSA. However, the legislative history of the CSA suggests the following in determining whether a particular drug or substance has a potential for abuse (Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No 91-1444, 91st Cong., Sess.1 (1970) reprinted in U.S.C.C.A.N. 4566, 4603):

a. *Individuals are taking the drug or other substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community; or*
b. *There is a significant diversion of the drug or other substance from legitimate drug channels; or*
c. *Individuals are taking the drug or other substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs; or*
d. *The drug is so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions*

from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community. Of course, evidence of actual abuse of a substance is indicative that a drug has a potential for abuse.

In determining the abuse potential of any substance, multiple factors must be considered. These include prevalence and frequency of use in the general public and in specific subpopulations, the amount of material that is available for illicit use, the ease with which the substance may be obtained or manufactured, the reputation or status of the substance "on the street" as well as evidence relevant to population groups that may be at particular risk. Animal data and epidemiological data are both used in determining a substance's abuse liability. Epidemiological data can also be an important indicator of actual abuse. Evidence of clandestine production and illicit trafficking of a substance are important factors to consider as this evidence sheds light on both the demand for a substance as well as the ease with which it can be obtained.

DEA considered all the available data in addition to information DHHS provided in their scientific and medical review document. DEA found that:

a. *Individuals are taking hydrocodone combination products in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.*

- Drug Abuse Warning Network (DAWN) data indicate that abuse of hydrocodone combination products has been associated with large number of admissions to the emergency department (ED). The rates of ED mentions per each kg of the drug of hydrocodone (as bitartrate salt form) combination products distributed were similar (during 1998 through 2002) or slightly lower (during 2004 through 2006) than those for oxycodone (as hydrochloride salt form) products.
- According to the Florida Department of Law Enforcement (FDLE), hydrocodone combination products have been associated with large number of deaths in Florida in recent years. For example, in 2007, hydrocodone combination products were associated with 807 deaths, while oxycodone products were associated with 1,253. The rates of deaths (deaths per 100 kg of drug distributed in Florida) associated with hydrocodone (as bitartrate salt form) combination products were similar to those for oxycodone (as hydrochloride salt form) products.
- According to the American Association of Poison Control Centers' National Poison Data System (NPDS; formerly known as Toxic Exposure Surveillance System or TESS), annual toxic exposures to hydrocodone combination products exceeded those to oxycodone products from 2002 through 2006. For example, in 2006, there were 22,244 toxic exposures for hydrocodone combination products and 13,417 for oxycodone products. Majority of exposures were of intentional reason for both drugs. The rates (exposures per 100 kg of drug distributed or per 1 million U.S. population) of toxic exposures to hydrocodone (as bitartrate salt form) combination products were higher than those to oxycodone (as hydrochloride salt form) products.

b. *There is significant diversion of hydrocodone combination products from legitimate drug channels.*

- According to the National Forensic Laboratory System (NFLIS), hydrocodone, similar to oxycodone, is among the top 10 most frequently encountered drugs in this system.
  - Total annual cases and drug exhibits for hydrocodone combination products analyzed by state and local forensic laboratories exceeded those for oxycodone products in recent years. In 2007, there were 25,034 cases and 29,447 exhibits for hydrocodone combination products and 18,709 cases and 22,782 exhibits for oxycodone products.
  - The rates of diversion (calculated as cases or exhibits per kilogram amounts of drug distributed) of hydrocodone combination products are similar to or slightly larger than those of oxycodone products.
- DEA has documented a large number of diversion and trafficking cases involving hydrocodone combination products. DEA cases involving hydrocodone combination products consistently exceeded those for oxycodone products from 2004 through 2007. Cumulative total cases for hydrocodone combination products and oxycodone products during this period were 1,146 and 878, respectively.
- DEA investigations show that hydrocodone combination products are being diverted from rogue Internet pharmacies.
  - Data from 71 suspect pharmacies (identified by DEA) for allegedly filling illegal Internet prescriptions, ordered a cumulative total of about 1,041 kg (as base form of the drug) of hydrocodone combination products from 2005 through 2007.
  - Average amounts of hydrocodone combination products distributed to the above mentioned 71 pharmacies were about 12-, 16- and 5-fold larger than that of its corresponding average amounts distributed to all pharmacies in the U.S in 2005, 2006 and 2007, respectively.
  - The differences between the above mentioned 71 pharmacies and all U.S. pharmacies with regard to the total annual amounts of other opioid products ordered were smaller than the corresponding differences for hydrocodone combination products ordered.

c. *Individuals are taking the drug or substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs.*

- According to the National Survey on Drug Use and Health (NSDUH), the incidence of non-medical use (lifetime and past year initiates) of hydrocodone combination products exceeded that of oxycodone products from 2002 through 2005. In 2005, the numbers of lifetime users and past year initiates for hydrocodone combination products were 18.9 and 1.3 million, respectively. The corresponding numbers for oxycodone products were 12.0 and 0.46 million. The rates of abuse (calculated as the number of past year initiates per kilogram of drug distributed) for hydrocodone (as bitartrate salt form) combination products were substantially higher than those for oxycodone (as hydrochloride salt form) products.
- According to the NSDUH, percentages of the lifetime users of hydrocodone combination products (range: 42.7% to 48.7%) reporting past year use of any pain reliever for non-medical purpose are higher than those of the lifetime users of oxycodone products other than OxyContin® (i.e., oxycodone immediate-release products) (range: 33.4% to 36.6%) from 2002 through 2006.

- According to the NSDUH, the combined data from 2002 through 2005 indicate that 57.7% of persons who first used pain relievers non-medically in the past year used hydrocodone combination products while 21.7% used oxycodone products.
- According to the MTF, the annual prevalence of non-medical use of Vicodin®, a hydrocodone combination product, was about 10% among high school seniors and exceeded that of OxyContin® (about 5%), an oxycodone extended-release product. The annual non-medical use of Vicodin® among 8th, 10th, and 12th graders in 2007 were 2.7, 7.2 and 9.6%, respectively. The corresponding numbers for OxyContin® were 1.8, 3.9 and 5.2%.

d. *The drug is related in its action to other substances already listed as having potential for abuse to make it likely that the drug will have the same potential for abuse as such drugs listed in schedule II.*

- Hydrocodone substance (schedule II) possesses abuse liability effects substantially similar to morphine (schedule II) in both animals and humans. Hydrocodone substitutes for morphine in opioid-dependent subjects.
- Two clinical abuse liability studies have demonstrated that hydrocodone combination products (Hycodan® or hydrocodone in combination with acetaminophen) were similar to morphine with respect to physiological effects, subjective effects, and drug "liking" scores.

Collectively these data demonstrate that hydrocodone combination products have a high potential for abuse similar to other schedule II opioid analgesic drugs. The following is the summary of the data DEA considered in making the above findings.

1.1. Abuse Liability Studies

Hydrocodone, also known as dihydrocodeinone, is a semisynthetic opioid drug. Hydrocodone, similar to morphine-like drugs, exerts its main pharmacological effects through binding to μ opioid receptors (Gutstein and Akil, 2006). Similar to other morphine-like drugs, hydrocodone produces analgesia, respiratory depression, miosis and reduction in gastrointestinal motility and has the potential of being abused.

1.1.1. Preclinical abuse liability

All preclinical screening for abuse liability has involved the hydrocodone substance and not hydrocodone combination products.

1.1.1.1. Drug discrimination

There is a strong correspondence between the discriminative stimulus effects of a given drug in animals and its subjective effects in humans. Thus, drug discrimination is widely used to determine whether or not a new test drug or substance is pharmacologically similar to a known drug of abuse. If the new drug or substance exhibits discriminative stimulus effects in animals

similar to a known drug of abuse, it is highly likely that this drug or substance shares subjective effects and would be similarly abused by humans.

Animals trained to discriminate the presence versus absence of morphine tend to respond on the morphine-appropriate lever in a dose-dependent fashion. Drugs that produce morphine-like effects in these animal models show a significant concordance with drugs that show an opioid profile when tested in human opioid abuser populations. Rats that have been trained to discriminate the presence versus absence of 3 mg/kg of morphine sulfate engender a dose- and time-dependent cross-generalization to hydrocodone (Tomkins *et al.*, 1997). The ED_{50} values for cross-generalization with the 3 mg/kg morphine training cue in these rats with 30 and 60 min pretreatment intervals were 0.5 and 0.7 mg/kg, respectively. Similar cross-generalization between morphine and hydrocodone was also reported in rhesus monkeys (France *et al.*, 1996). Similarly Lelas *et al.* (1999) studied the discriminative stimulus effects of hydrocodone in morphine-abstinent rhesus monkeys treated daily with morphine (3.2 mg/kg SC, prior to each session) and trained to discriminate naltrexone (0.01 mg/kg, SC) and vehicle. Hydrocodone (ED50 = 0.37 mg/kg, SC), similar to morphine (ED50 = 1.76 mg/kg, SC) and hydromorphone (ED50 = 0.25 mg/kg, SC), dose-dependently decreased naltrexone-appropriate responding. Naltrexone dose-dependently shifted the dose-effect curve for morphine-like discriminative stimulus effects of hydrocodone to the right. Authors suggested that the discriminative effects of hydrocodone, similar to hydromorphone, are due mainly to their activity at μ opioid receptors. The above mentioned data suggest that hydrocodone and morphine are likely to produce similar profile of subjective effects in humans and to possess similar abuse potential.

1.1.1.2. Drug self-administration

Drugs that function as positive reinforcers in animal models are generally considered to have abuse liability in humans. A strong correlation exists between those drugs that are self-administered by laboratory animals and those that are abused by humans. Self-administration of drugs by animals has been utilized to assess positive reinforcing properties and as a preclinical predictor of abuse liability of most dependence-producing drugs (Schuster and Thompson, 1969) with the possible exception of hallucinogenic substances (Deneau et al., 1969).

Animals are typically trained to work (lever press, nose poke etc.) to receive a single intravenous bolus injection of drug as a potential reward. Drugs that initiate and/or maintain lever-press responding above those levels engendered by saline administration are considered to produce a reward or motivation to continue to self-administer the drug. The self-administration task has been used to predict those drugs that would be classified as opioid-like or "addictive" in the human population (Brady and Lukas, 1984). Hydrocodone has been found to both initiate and maintain lever-press responding in rats at a dose of 0.16 mg/kg per injection (Tomkins *et al.*, 1997). The dose-dependent changes in the number of self-infusions administered in hourly test sessions were similar to those seen when morphine was self-administered in rats.

1.1.1.3. Morphine-like withdrawal effects

Deneau & Seevers (1955), reported that hydrocodone (Dicodid, dihydrocodeinone), is similar to hydromorphone (Dilaudid®) in suppressing the abstinence signs elicited by chronic

administration followed by abrupt withdrawal of morphine (3 mg/kg every 6 hours for 8 to 12 months) in monkeys. These authors further showed that abrupt drug withdrawal following prolonged daily administration of hydrocodone (0.75 mg/kg, every four hours for 30 days); similar to other opioid analgesic drugs including morphine and hydromorphone, elicits abstinence signs in monkeys. Nalorphine, an opioid antagonist, induced abstinence signs in these monkeys. These authors concluded that these results were similar to those results obtained in humans (Seevers and Deneau, 1956).

In 1959, Deneau, McCarthy, & Seevers suggested that the rate and intensity of development of physical dependence (as measured by the intensity of abstinence and the capacities of various drugs, in comparison with morphine, to initiate physical dependence or to suppress abstinence) in monkeys are similar to those in man and these can be assessed objectively. Deneau, McCarthy & Seevers (1959) established a "monkey index" and "man index" and then, for comparison purposes, developed a correlation ratio between the two in an attempt to quantify the abuse liability of various opioid compounds. Using this analytical approach, these authors found that hydrocodone is more potent than morphine in suppressing morphine abstinence in monkeys and equipotent to morphine in man.

Preclinical abuse liability summary

Discriminative stimulus effects of hydrocodone are similar to those of morphine in animal models. Hydrocodone is self-administered in animal models. Hydrocodone, similar to morphine and hydromorphone, suppresses withdrawal effects of morphine. Hydrocodone, similar to morphine and hydromorphone, upon abrupt drug withdrawal following its daily administration, elicits opioid abstinence signs in monkeys and nalorphine induces abstinence signs in these animals. These data collectively suggest that hydrocodone substance has an abuse liability similar to morphine.

1.1.2. Clinical abuse liability

1.1.2.1. Hydrocodone substance

In 1939, the Advisory Committee on Traffic in Opium and Other Dangerous Drugs in their report to the League of Nations stated that hydrocodone (Dicodid) produces euphoria and addiction similar to that of morphine.

Fraser and Isbell (1950) investigated abuse liability of hydrocodone in three separate clinical studies. These studies demonstrated; (1) in former morphine addicts, 20 mg of hydrocodone administered intravenously (IV) or subcutaneously (SC) produced a grade of euphoria equivalent to that induced by 30 mg of morphine; (2) Hydrocodone (45 mg) produced a sharp decline in the intensity of the opioid withdrawal syndrome for 6 to 8 hours after its administration in two morphine (chronically administered 480 mg per day) dependent subjects undergoing spontaneous withdrawal; and (3) In five male subjects with a history of morphine addiction maintained on 240 mg (60 mg q.i.d., SC) hydrocodone produced physiological (miosis and EEG changes) and subjective (drug liking) effects similar to those of morphine. Upon abrupt withdrawal of hydrocodone, these subjects experienced withdrawal syndrome similar, but

milder, than that of morphine, but more pronounced than that of codeine. Based on these data, these investigators concluded that the abuse potential of hydrocodone is more similar to morphine than to codeine (Isbell, 1949; Fraser and Isbell, 1950).

Jasinski and Martin (1967), using double-blind cross-over design study, compared the dependence-producing properties of hydrocodone and codoxime to morphine in 10 male volunteers. Subjective effects were assessed for 12 hours following intramuscular administration of these drugs. Time-effect functions were assessed for the first four hours after single drug test sessions for mean pupillary constriction, opioid signs, opioid symptoms, "liking" scores (assessed by the research technicians), and "liking" scores (assessed by the subjects). All measures from these acute dose tests indicated that hydrocodone and morphine were equipotent and produced equivalent drug-effects. There were no marked differences among the time-effect functions of the three drugs tested and all effects showed dose-response functions, as well. To further examine the opioid-like nature of hydrocodone, the drug was tested for its ability to suppress the signs and symptoms of opioid abstinence syndrome in seven additional subjects chronically administered 240 mg of morphine sulfate per day. Abstinence was assessed from the 14th through the 24th hour after the last dose of morphine was administered using an 11-point scale. Hydrocodone was able to substitute for morphine and diminish the intensity of the abstinence syndrome, evidence defined by the authors as a measure of the physical dependence producing properties of hydrocodone.

Kaplan et al. (1997) investigated the abuse liability related subjective effects of orally administered hydrocodone (10, 15 and 22.5 mg) in a selected group of recreational drug users who showed a positive response to hydromorphone (SC) on several subjective effects. Hydrocodone produced pleasant effects and increased drug liking score as compared to placebo. It also produced increases in unpleasantness-dysphoria scale.

Walsh et al. (2008) using a double-blind, randomized, within-subject, placebo-controlled design examined the relative abuse potential and potency of oral oxycodone (10, 20, and 40 mg), hydrocodone (15, 30, and 45 mg), hydromorphone (10, 17.5, and 25 mg) and placebo in nine healthy volunteers with history of sporadic prescription opioid abuse. These authors found that all three opioid analgesics produced a profile of pharmacological effects that are typical of μ opioid receptor agonists and these effects are dose-dependent. These included subjective effects such as increased ratings of liking, good effects, high and opioid symptoms, observer-rated measures (skin itchy, relaxed, coasting, talkative, drunken, nodding, sluggish, friendly and energetic) and physiological effects (miosis, modest respiratory depression, exophoria, decrements in the visual threshold discrimination). These investigators also found that supratherapeutic doses of these drugs tested were well tolerated by the subjects with only modest changes in respiratory function

Walsh et al. (2008) also found no substantive differences in their onset of action for these drugs. All three drugs produced similar abuse liability related subjective effects. Percent of subjects identifying test drugs as opioids were similar for all these drugs. For example, 89, 89, and 100% of subjects who received 15, 30, and 45 mg hydrocodone respectively identified it as opioid. Similarly 56, 67, and 100% of subjects who received 10, 20, and 40 mg oxycodone respectively identified it as opioid. The corresponding numbers for 10, 17.5, and 25 mg

hydromorphone were 78, 89, and 100%. These authors also found that oxycodone was approximately equipotent to or slightly more potent than hydrocodone. Hydromorphone was modestly more potent (less than two-fold) than either oxycodone or hydrocodone. These authors concluded that abuse liability profile and relative potency of these three opioids do not differ substantially from one another.

1.1.2.2. Hydrocodone combination products

The DHHS review document mentioned that several combination products containing hydrocodone in combination with nonnarcotic substances such as acetaminophen, aspirin, ibuprofen, chlorpheniramine, or homatropine are currently marketed as analgesics or cough suppressants. DHHS review provided two clinical rationales for the current less restrictive schedule of hydrocodone combination products (schedule III) as compared to hydrocodone substance (schedule II). One rationale cited was that combination of nonnarcotic analgesics with opioid analgesic reduces the amount of opioid needed in a unit dose to produce a desired degree of analgesia (Beaver, 1984). As a consequence, a proportionate reduction in the other pharmacological effects (including euphoric effects) of opioid analgesics present in these combination products is thought to occur. Although this is a favorable scenario for a patient who is not a drug abuser, it is unlikely to be a deterrent for the typical drug abusers from abusing these drug formulations as this scenario can be overcome by increasing the number of unit doses ingested. Further, some hydrocodone combination products contain nonnarcotic substance that is not analgesic (e.g. Hycodan® containing homatropine). Thus the above rationale of analgesia potentiation does not apply to all hydrocodone combination products.

The second rationale cited in the DHHS review document was that the nonnarcotic active ingredient present in hydrocodone combination products produce toxic, dysphoric, and unpleasant effects upon ingestion of high doses and thus lower the potential for abuse of these products. The current unprecedented and continuing high prevalence of abuse of hydrocodone combination products do not support the rationale that the *toxic* effects of high doses of nonnarcotic ingredients of these products lessen the abuse potential of these products. Further, as discussed later in this section, two recent clinical studies show that both pleasant and unpleasant subjective effects of hydrocodone combination products were largely similar to those of μ opioid receptor agonists, morphine and oxycodone in recreational abusers (Zacny, 2003; Zacny *et al.*, 2005; Walker and Zacny, 1999; Hill and Zacny, 2000; Zacny and Gutierrez, 2003; Zacny and Lichtor, 2008). In contrast, mostly pleasant and very few if any unpleasant effects are usually found when μ opioids are administered to opioid abusers (Preston and Jasinski, 1991; Dykstra *et al.*, 1997; Walsh et al., 2008). These differences have been thought to be due to differences in study populations in regard to their opioid use and differential tolerance. Further, Zacny et al. (2005) and others (Eade and Lasagna, 1967; Bradley and Nicholson, 1987; Pickworth et al., 1991; Zacny and Gutierrez, 2008) found that nonnarcotic analgesics such as acetaminophen have no measurable psychoactive (either pleasant or unpleasant) effects when administered alone. These studies taken together with the high prevalence of actual abuse of hydrocodone/acetaminophen combination products as described in the later part of this document do not support this rationale about the abuse deterrent effects of *dysphoric or unpleasant* effects, if any, of the nonnarcotic drugs present in these products.

Zacny (2003) characterized the subjective, psychomotor, and physiological effects of a hydrocodone combination product (Hycodan®) in volunteers with history of recreational drug use, but no history of drug dependence. Eighteen volunteers participated in a crossover, randomized, double-blind study in which they received orally administered placebo, 5 mg hydrocodone/1.5 mg homatropine, 10 mg hydrocodone/3 mg homatropine, 20 mg hydrocodone/ 6 mg homatropine, 40 mg morphine and 2 mg lorazepam. Measures were assessed before and for 300 minutes after drug administration. End-of-session and 24-hour measures were taken to assess residual drug effects and overall subjects' assessment of the drug effects. Subjective effects of Hycodan® were dose-related, with the majority of statistically significant effects occurring following the highest dose combination tested. Hycodan®, following low dose (5 mg of hydrocodone/1.5 mg homatropine), lacked subjective and psychomotor impairing effects. The combination of 20 mg hydrocodone/6 mg homatropine produced subjective effects similar to those of 40 mg morphine. Both drugs produced largely similar pleasant (including drug liking) as well as unpleasant subjective effects. Morphine and other μ-opioid analgesics have been shown to produce similar pattern of both pleasant and unpleasant effects (Walker and Zacny, 1999; Hill and Zacny, 2000; Zacny and Gutierrez, 2003; Zacny and Lichtor, 2008). These authors further found that Hycodan®, unlike morphine, decreased "hungry" ratings and heart rate presumably due to homatropine's effects. The decrease in heart rate was mentioned as clinically irrelevant. These authors stated that the extent to which these peripheral presumably anticholinergic effects of homatropine affected the abuse liability related subjective effects measures in their study is not known and further studies are needed to address this issue.

Zacny *et al.* (2005) using a crossover, randomized, double-blind study investigated the abuse liability-related subjective effects of different dose strengths of hydrocodone/ acetaminophen combination product in comparison with 40 mg morphine, 1000 mg of acetaminophen and placebo in 18 volunteers (recreational drug users with no history of drug dependence). Hydrocodone/acetaminophen combination product, similar to morphine, dose-dependently elicited both abuse-liability related subjective effects and some unpleasant effects. Hydrocodone (20 mg)/acetaminophen (1000 mg) combination produced effects that were similar in magnitude to that of 40 mg morphine. The low dose of hydrocodone (5 mg)/acetaminophen (500 mg) combination did not significantly alter subjective effects measures. Acetaminophen by itself did not produce any measurable psychotropic effects. Morphine, but not hydrocodone/acetaminophen combination, produced significant increases in ratings of "dry mouth", "tingling", and "feel bad" (in females only) and significant reductions in ratings of "in control of body" (in females only). The highest dose of hydrocodone combination product (20 mg hydrocodone/1000 mg acetaminophen) produced unpleasant effects such as increases in ratings of "confused", "difficulty concentrating", "dizzy", "having unpleasant bodily sensations", "heavy or sluggish feeling", "nauseous" and "turning of the stomach". This pattern of both abuse liability-related effects as well as unpleasant effects of hydrocodone/acetaminophen combination product has also been noted with morphine and other μ opioids (Walker and Zacny, 1999; Hill and Zacny, 2000; Zacny and Gutierrez, 2003). Ratings of "heavy or sluggish feeling", "light headed", "sedated" and "floating" produced by morphine lasted considerably longer than that of hydrocodone (20 mg)/acetaminophen (1000 mg) combination product. Both hydrocodone combination product (20 mg hydrocodone/1000 mg acetaminophen) and morphine impaired psychomotor performance and produced miosis. Some subjects 24 hours post-session in one or more of the hydrocodone/acetaminophen combination

condition and/or morphine conditions reported liking and wanting to take the drug again on another session, if given the opportunity. These authors concluded that abuse liability-related subjective effects of hydrocodone/ acetaminophen combination product are in accordance with the widespread non-medical use and abuse of this combination product.

DHHS review document stated the following argument with regard to highest dose of hydrocodone used in the clinical study of Zacny *et al.* (2005), "At the highest dose tested of 20 mg of hydrocodone and 1000 mg of acetaminophen, the combination produced similar effects to those of 40 mg of morphine. Were this combination an approved product, it would be listed in Schedule II because the amount of hydrocodone is outside the specified amount required for Schedule III product." Thus, DHHS concluded that the currently marketed hydrocodone combination products have lower abuse potential.

However, the above interpretation is incorrect. The maximum allowable amount of hydrocodone in a schedule III hydrocodone combination product is 15 mg as the free anhydrous base which is equivalent to 24.59 mg of bitartrate salt of hydrocodone. Zacny *et al.* (2005) used the bitartrate salt of hydrocodone in their study. Therefore, the 20 mg of hydrocodone bitartrate utilized in this study is within maximum limits for a schedule III hydrocodone combination product. Zacny et al. (2005) found that the abuse related subjective effects of 20 mg hydrocodone/100 mg acetaminophen combination are similar to those of 40 mg of morphine.

DHHS review cited another clinical study by Zacny (2003) who showed that Hycodan®, a hydrocodone combination product containing homatropine, produced both pleasant and unpleasant effects. DHHS further extrapolated these findings by suggesting that unpleasant effects of nonnarcotic ingredient present in this combination product may limit its abuse potential. Contrary to this interpretation of DHHS, the original publication (Zacny, 2003) stated that the subjective effects (both pleasant and unpleasant effects) of hydrocodone combination product, Hycodan®, are similar to those of morphine and other μ opioid agonists. This author further stated that the extent to which peripheral presumably anticholinergic effects (reduction in heart rate and "hungry" ratings) of Hycodan® (due to homatropine) affected the abuse related subjective effects measures in this study is not known and further studies are needed to address this issue. The main conclusion of Zacny's study was that Hycodan® at the highest dose tested produce effects similar to those of 40 mg of morphine.

Clinical abuse liability summary

Hydrocodone, similar to morphine, produces euphoria and suppresses opioid withdrawal syndrome. Hydrocodone is more potent than morphine in suppressing morphine abstinence syndrome in monkeys but is equipotent in suppressing the syndrome in man. In comparison, Dilaudid (hydromorphone hydrochloride) was found to be less potent than morphine in both monkey and man. Hydrocodone, similar to morphine, produces opioid withdrawal syndrome.

Hydrocodone combination products (Hycodan® or hydrocodone in combination with acetaminophen) are similar to morphine with respect to physiological effects, subjective effects, and "liking" scores. Acetaminophen, the nonnarcotic analgesic ingredient present in majority of the currently marketed hydrocodone combination products, at clinically relevant doses lacks

psychoactive effects.

Abuse liability summary

In summary, hydrocodone can substitute for morphine in opioid-dependent subjects and produces effects substantially similar to morphine in both animals and humans. These data are consistent with the placement of hydrocodone substance in schedule II of the CSA based on abuse potential, medical use and dependence profile. However, there are no scientific clinical studies published in the medical literature that demonstrated lower abuse potential of hydrocodone combination products relative to its substance, to other standard opioid analgesic drugs (e.g., morphine, hydromorphone and oxycodone), or to other opioid combination products. Thus, there is no published scientific and clinical basis for placing hydrocodone combination products in schedule III. On the contrary, the two recent published clinical studies found that the abuse liability related subjective effects of hydrocodone combination products, namely Hycodan® and hydrocodone in combination with acetaminophen, are similar to those of morphine, a schedule II opioid analgesic (Zacny, 2003; Zacny *et al.*, 2005).

Therefore, the DHHS review document taken together with the detailed conclusions of authors and the expanded statistical analysis of the actual abuse data using actual drug amounts distributed and total patient-days of therapy as denominators (representing drug availability) as presented in the following section demonstrate that the potential for abuse of hydrocodone combination products is similar to that of schedule II opioid products.

1.2. Actual Abuse

The diversion, trafficking and abuse of hydrocodone in the U.S. refer to its combination products as no single-entity hydrocodone products are currently marketed, while that of oxycodone refer both to its single-entity and combination products. The diversion, trafficking and abuse of hydrocodone and oxycodone are mainly associated with pharmaceutical products manufactured, distributed and prescribed within the U.S. There is no clandestine production of these substances. The production and prescription of these products have increased dramatically in recent years. Various data sources indicate that hydrocodone combination products as well as oxycodone products are extensively diverted and abused and are associated with considerable morbidity/mortality.

1.2.1. Rationale for selection of oxycodone as the reference standard drug for use in evaluating the current petition

Both hydrocodone and oxycodone are high-efficacy μ opioid receptor agonists (Chen *et al.*, 1991; Kotzer *et al.*, 2000; Gutstein and Akil, 2006) and are controlled as schedule II substances under the CSA. Hydrocodone bitartrate is equipotent to oxycodone hydrochloride on a milligram basis as oral analgesics (Gutstein and Akil, 2006). Similarly, hydrocodone bitartrate has been shown to be approximately equipotent or slightly less potent than oxycodone hydrochloride on milligram in producing abuse liability related subjective effects (Walsh et al., 2008). Both hydrocodone and oxycodone are marketed in combination with nonnarcotic analgesics. About 90% of all prescriptions for hydrocodone combination products contain acetaminophen and, likewise, over 90% of prescriptions for all oxycodone combination products

contain acetaminophen (IMS Health, National Prescription Audit *Plus*™, years 2002 through 2007, Data extracted September 2008, (NPA*Plus*™)). Although oxycodone combination products, without the inclusion of its single-entity products, are ideal reference drugs for the present evaluation, this comparative analysis is not possible since majority of the currently existing drug abuse databases do not provide product-, formulation- (immediate-release versus extended-release products) and composition- (single-entity versus combination products) specific data. Thus, the drug abuse data, with the exception of NSDUH and Adverse Event Reporting System (AERS) data, for oxycodone products in its entirety in comparison with those of hydrocodone combination products were used in the present evaluation. DEA obtained from the Substance Abuse and Mental Health Services Administration (SAMHSA) and FDA some product-specific NSDUH and AERS data for OxyContin®, an extended-release oxycodone product. Accordingly DEA analyzed NSDUH and AERS data for oxycodone products with and without the inclusion of OxyContin® data. The results of these comparative analyses are presented in the present review document.

DHHS evaluated abuse potential and dependence profile of hydrocodone combination products by selecting other narcotic analgesic products (pain relievers) namely oxycodone (schedule II) and propoxyphene (schedule IV) in combination with codeine (schedule III/V) as reference comparator drugs. However, the usefulness of codeine and propoxyphene as comparator drugs was restricted by the limited data available for these drugs. The NSDUH data for codeine and propoxyphene, as mentioned in the DHHS review document, was not in the drug-specific format. Instead, these data were combined under one category of *codeine or propoxyphene*, presumably due to the fact that the NSDUH survey combined these two drugs into one broad category in its data collection thus precluding drug-specific analysis. Although the DHHS review document provided data from AERS for codeine and propoxyphene separately, it also cited major limitations of this database.

1.2.2. Selection of appropriate denominators (representing drug availability) for use in calculating rates of drug abuse

There is considerable discussion among epidemiologists about the methods to calculate rates of abuse and adverse health effects resulting from abuse of opioid pharmaceuticals (Dasgupta *et al.*, 2006; Hughes *et al.*, 2007; Cicero *et al.*, 2005, 2007a, 2007b; Passik and Kirsh, 2007; Smith *et al.*, 2007). In the past, epidemiologists have used several different denominators such as total prescriptions, total populations, potency-adjusted total kilograms of opioids, and total number of patients prescribed etc. to calculate drug abuse rates. The types of inferences that can be drawn from such analyses depend upon the nature of denominator used.

DHHS, in its scientific and medical evaluation, used the total number of prescriptions (obtained from commercially available prescription database) as a denominator to calculate rates of abuse of opioid products. DHHS calculated the rates of abuse, by dividing the reported numbers of drug abuse or misuse incidences, and its related adverse health consequences (Emergency Department (ED) mentions) by total number of prescriptions. DHHS used these rates as key parameters to assess the abuse potential of hydrocodone combination products relative to other opioid products.

DHHS evaluated the abuse potential of a given opioid drug by calculating rates of its abuse and abuse related adverse health consequences relative to its total prescriptions as an indicator of its availability. Upon reviewing this and careful consideration of numerous other factors, DEA expanded this analysis by selecting two additional denominators also as indicators of drug availability and used the same to calculate rates of abuse of a given drug. These denominators include total patient-days of therapy (data derived from NPA*Plus*™) and drug distribution (sales) data as reported in the Automation of Reports and Consolidated Orders System (ARCOS), a DEA database that tracks the distribution and sale of all schedule II and schedule III narcotic drug products to all end-users (e.g., pharmacies, hospitals, physicians, teaching institutions and Opioid Treatment Centers). The reasons for the selection of these additional denominators and their detailed descriptions are discussed below.

1.2.2.1. "Total Prescriptions" as a denominator (representing drug availability)

For the comparative evaluation involving two or more drugs, total prescriptions is a valid measure of drug availability provided these drugs are similar with regard to the primary variable such as average days of therapy per prescription and secondary variables such as drug-specific differences in composition-type (single-entity versus combination products) and formulation-type (e.g., immediate-release versus extended-release products), total dosage units per prescription, potency-adjusted drug amounts per each dose unit and in clinical indications (the intended patient population). As described below, the comparative analysis of prescriptions for hydrocodone and oxycodone products demonstrate that both these drugs differ largely in this regard.

According to the prescription data from IMS Health, IMS National Sales Perspectives™ (January 2002 through December 2007, Retail Channels, Data Extracted September 2008), in 2007, nearly 100% of the total amount (kg) of hydrocodone dispensed was for combination products, while oxycodone was dispensed as both combination as well as single-entity immediate-release and single-entity extended-release products. Unlike hydrocodone, oxycodone combination products, which represented 68.8% of prescriptions for all oxycodone formulations, but accounted for only 27.2% of the total amount (kg) of oxycodone distributed in 2007. On the contrary, oxycodone single-entity products, which represented only about 31% (13% immediate-release and 18% extended-release) of prescriptions for all oxycodone formulations, represented the majority (72.7%) of the total quantity (kg) of oxycodone distributed in 2007 (Tables 1 and 2).

According to the NPA*Plus*™, about 90% or more of total of prescriptions for hydrocodone and oxycodone consisted of oral solid dosage formulations. Prescriptions for oxycodone single-entity immediate-release and extended-release products, oxycodone combination products, and hydrocodone combination products all differ from each other with regard to average number of dosage units present in each prescription (Table 2). For example in 2007, prescriptions for hydrocodone combination and oxycodone combination products, excluding liquids, had an average of 50.8 and 56.6 dosage units per prescription and 121.9 and 31.4 million prescriptions were dispensed for these products. Immediate-release (excluding liquids) and extended-release products containing oxycodone as a single-entity averaged 102.6 and 73.5 dosage units per prescription, respectively. Corresponding prescriptions for these were 6.0 and 8.1 million.

Table 1. Total quantities (in kilograms) of hydrocodone and oxycodone products distributed (sold) in the U.S. (IMS Health, National Sales Perspectives™, January 2002 through December 2007, Retail Channels, Data Extracted September 2008)

Drug	Product type	2002	2003	2004	2005	2006	2007
Hydrocodone	All products	31,297.2	36,280.8	39,656.2	44,151.9	47,757.8	52,205.7
	Combination products	31,295.5	36,276.5	39,653.0	44,149.2	47,755.1	52,204.0
	Single-entity products	1.7	4.2	3.2	2.6	2.7	1.7
Oxycodone	All products	26,861.7	31,056.5	33,496.7	37,075.7	42,182.3	48,088.3
	Combination products	6,520.3	7,842.9	8,980.7	10,266.6	11,670.4	13,102.1
	Single-entity products	20,341.4	23,213.5	24,516.0	26,809.1	30,511.9	34,986.1

Table 2. Total prescriptions (expressed in thousands) and average number of dosage units per each prescription (shown in parentheses) for hydrocodone and oxycodone products (NPA*Plus*™, from 2002 through 2007, data extracted September 2008)

Drug	Product type	2002	2003	2004	2005	2006	2007
Hydrocodone	All products	102,329	110,222	114,491	123,356	129,697	135,466
	Oral solid products (exclude liquids)	88,394 **(41.3)**	95,236 **(43.6)**	101,906 **(45.6)**	108,023 **(47.1)**	115,657 **(49.1)**	121,911 **(50.8)**
Oxycodone	All products	29,387	32,523	34,790	37,895	42,292	45,878
	Combination oral solid products	19,873 **(45.9)**	22,022 **(48.5)**	24,011 **(50.9)**	26,547 **(53)**	29,366 **(54.5)**	31,404 **(56.6)**
	Single-entity extended-release oral solid products	7,112 **(69.8)**	7,561 **(70.64)**	7,294 **(72)**	7,153 **(72.77)**	7,599 **(73)**	8,078 **(73.5)**
	Single-entity immediate-release oral solid products (exclude liquids)	2,114 **(96)**	2,642 **(97.9)**	3,165 **(100.3)**	3,841 **(100.1)**	4,948 **(99.4)**	5,997 **(102.6)**

According to the Automation of Reports and Consolidated Orders System (ARCOS), oxycodone single-entity products, oxycodone combination products, and hydrocodone combination products differ from each other with regard to average drug amount present in each dosage unit sold (Table 3). For example, in 2007, hydrocodone combination products,

oxycodone single-entity products and oxycodone combination products that were distributed to end-users had average drug amounts of 7.3, 23.2, and 6.5 milligrams (mg) per each dosage unit, respectively. Thus the average drug amounts present in each dosage unit of single-entity oxycodone products (range: 23.1 - 24 milligrams per dosage unit) were about 3.5 to 4-fold larger than that in oxycodone combination products (range: 5.8 - 6.5 milligrams per dosage unit) distributed from 2003 through 2007. Unlike oxycodone, all hydrocodone products are marketed as combination products with average drug amounts of 7.1 - 7.3 milligrams per each dosage unit during this period. Total amounts of oxycodone distributed annually as single-entity products accounted for over 70% of its total amounts distributed from 2003 through 2007.

Table 3. Annual distribution data for hydrocodone and oxycodone products§ (ARCOS)

Drug	Measure	2003	2004	2005	2006	2007
Hydrocodone	Total drug (salt form) amount (Kg) in all products	36,626	39,479	42,302	48,944	54,051
	Total DUs*	4,468,152	5,323,161	5,638,637	6,416,316	7,070,846
	Average drug amount (mg) per each DU	*7.1*	*7.2*	*7.2*	*7.3*	*7.3*
Oxycodone	Total drug (salt form) amount in kilograms (Kg) in all products	29,617	32,419	34,032	41,149	47,753
	Total dosage units (DU)*	2,191,835	2,413,556	2,584,776	3,078,790	3,511,028
	Total drug (salt form) amount (Kg) in single-entity (SE) products	21,732	23,528	24,388	29,224	33,949
	Single-entity (SE) DU*	913,940	984,052	1,051,926	1,267,707	1,468,173
	Average drug amount (mg) per each DU (SE)	*23.9*	*24.0*	*23.3*	*23.1*	*23.2*
	Combination products (CP) DU*	1,277,895	1,429,504	1,532,850	1,811,083	2,042,854
	Average drug amount (mg) per each DU (CP)	*5.8*	*6.0*	*6.1*	*6.3*	*6.5*

§ The vast majority of oxycodone products are formulated in the hydrochloride salt form while hydrocodone combination products are primarily formulated in the bitartrate salt. Thus the molecular weights of these two salt forms were used for conversion from the base to the corresponding salt form

*Data expressed in thousands of dosage units; excludes liquid formulations for hydrocodone

Thus, hydrocodone combination products and oxycodone products differ from each other with regard to types of dosage formulations and product composition, average number of dosage units per prescription and average drug amount per dosage unit. Further, most importantly, total number of prescriptions when used as denominator does not account for one important and primary variable such as the total number of days of therapy for these prescriptions. Therefore, total number of prescriptions as a measure of drug availability (as a denominator) is of limited use in comparing hydrocodone versus oxycodone products.

1.2.2.2. Total patient-days of therapy as a denominator (representing drug availability)

For the present evaluation, DEA utilized total patient-days of therapy, an expanded version of total prescriptions, as a denominator to calculate rates of drug abuse (Table 4). Total patient days of therapy is defined as the total number of days for which annual prescriptions for a given opioid drug are expected to provide treatment for all patients who are prescribed the same opioid drug. Unlike total number of prescriptions, total patient-days of therapy, as defined above, takes into account not only the total number of prescriptions but also duration of their availability for its use and its potential abuse and for diversion. Thus DEA selected total patient-days of therapy as a denominator to represent drug availability and used it in calculating rates. Patient-days of therapy for a given opioid drug product were calculated by multiplying its total number of prescriptions by the average days of therapy per prescription (as derived from NPA*Plus*™) for the same. Total patient-days of therapy for a given opioid drug were calculated as the sum of the patient-days of therapy for all products containing the same drug (Table 4).

Table 4. Annual total patient-days of therapy for hydrocodone and oxycodone products[Φ,§]

Year	Total Patient-Days of Therapy* (in Thousands)	
	Hydrocodone	Oxycodone
1998	496,569	158,435
1999	587,791	211,326
2000	661,777	288,544
2001	755,008	350,793
2002	851,393	391,543
2003	900,187	445,639
2004	981,437	483,288
2005	1,128,031	521,955
2006	1,275,681	600,291
2007	1,368,891	678,985

*Total prescriptions multiplied by average number of days of therapy per prescription.

Φ Average days of therapy were obtained from NPA*Plus*™ from 1998 through 2007, data extracted September 2008.

§In the U.S., nearly 100 percent (of total kilogram amounts distributed) of hydrocodone was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone was marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

It is important to note that total patient-days of therapy addresses the primary variable namely number of days of therapy per prescription, but not the secondary variables such as differences in composition-type (single-entity versus combination) and formulation-type (e.g., immediate-release versus extended-release), product strengths, dosage units per prescription and in clinical indications (thus intended patient population) etc.

1.2.2.3. Drug distribution (sales) data from ARCOS database as a denominator (representing drug availability)

DEA also utilized drug distribution (sold) data from ARCOS database as a denominator to calculate rates of drug abuse. The rationale for this selection is based on the following two primary reasons.

The first reason is to test the supposition that the nonnarcotic active ingredients present in hydrocodone combination products reduce the abuse potential of hydrocodone. From 2002 through 2007, ARCOS reported that nearly 100% (of kilogram amounts) of hydrocodone was distributed as pharmaceutical formulations that contained hydrocodone in combination with several nonnarcotic active ingredients (mainly acetaminophen in over 90% of total prescriptions for hydrocodone). In contrast, only about 24 through 28% (of total kilogram amounts) of oxycodone was sold as its combination products (mainly in combination with acetaminophen). Thus, majority (over 70% total kilogram amounts distributed) of oxycodone was sold as single-entity pharmaceutical products. Thus, if the supposition that the nonnarcotic active ingredients (e.g. acetaminophen) present in hydrocodone combination products reduces the abuse potential of hydrocodone were to be true, rates of abuse of hydrocodone combination products per each kilogram distributed would be lower than the corresponding numbers for oxycodone products.

The second reason is that the drug distribution data from ARCOS database, unlike total number of prescription and total patient-days of therapy, as a denominator, eliminate variability related to drug-specific differences such as product composition (single-entity versus combination) and formulation (immediate-release versus extended-release), total dosage units per prescription, and drug amounts per dosage unit. If a drug is not clandestinely produced, drug distribution data, as reported in ARCOS database, account for the total amount of a given drug consumed for both medical and non-medical purposes. DEA has no evidence that suggest either hydrocodone or oxycodone is clandestinely produced. Commercially available prescription databases do not capture data from all potential sources. For example, NPA*Plus*™, a prescription database, does not sample data from dispensing physicians, hospital pharmacies, clinic pharmacies, closed-wall HMOs and home healthcare facilities. These prescription databases also do not account for drug amounts that are diverted from pharmacies, hospitals, and physicians' offices. In contrast, ARCOS database does account for both these sources.

ARCOS does not account for drug amounts that are available for drug abusers from foreign sources. However, DEA has no information or data to suggest that either hydrocodone or oxycodone products are illicitly obtained from foreign sources in any significant amounts. Because the U.S. produces and consumes over 99% of total amount of hydrocodone produced in the world, foreign sources, if any, would be minimal for hydrocodone. Similarly, the U.S. is the major consumer (80% of total consumption in the world) of oxycodone.

In using ARCOS data as an indicator of drug availability, it is assumed that what is distributed to pharmacies, doctors, and hospitals is prescribed or dispensed to patients or otherwise diverted for non-medical use. In general, pharmacies and hospitals order drugs frequently (often on a weekly or monthly basis) and do not stockpile. Although there is a slight lag time between drug distribution and its actual use, a yearly distribution amount is very close

to the amounts utilized.

To summarize, the drug distribution (sale) data (from ARCOS), when used as a denominator to calculate drug abuse rates, allows to test of the supposition that the nonnarcotic ingredients present in hydrocodone combination products deter the abuse of these products. It also eliminates variability related to product-, form- and composition-specific differences between drugs as well as the differences in the total dosage units per prescription and drug amounts per dosage unit.

Table 5. Total annual consumption (kg) and consumption (g) per 100,000 U.S. populations of hydrocodone and oxycodone from 1997 through 2007*,§ (ARCOS).

Year	Total Annual Consumption of Hydrocodone Salt Form (Kg) Base Weight/0.61	Annual Consumption of Hydrocodone Salt Form per 100,000 U.S. Population (Grams)	Total Annual Consumption of Oxycodone Salt Form (Kg) Base Weight/0.9	Annual Consumption of Oxycodone Salt Form per 100,000 U.S. Population (Grams)
1997	14,212	5,326	4,944	1,853
1998	17,032	6,383	7,311	2,740
1999	19,839	7,143	10,797	3,887
2000	23,145	8,333	17,007	6,123
2001	25,565	9,204	22,141	7,972
2002	30,846	11,109	24,863	8,951
2003	36,627	13,187	29,617	10,663
2004	39,479	14,213	32,419	11,672
2005	42,301	15,230	34,032	12,253
2006	48,945	17,622	41,149	14,815
2007	54,050	19,460	47,753	17,193

* The vast majority of oxycodone products are formulated in the hydrochloride salt form while hydrocodone combination products are primarily formulated in the bitartrate salt. Thus the molecular weights of these two salt forms were used for conversion from the base to the corresponding salt form.
§In the U.S., nearly 100 percent (of total kilogram amounts distributed) of hydrocodone was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone was marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

For all of the afore-mentioned reasons, DEA concluded that ARCOS distribution (sale) data (Table 5) provide a valid indicator of drug availability. Hydrocodone bitartrate is equipotent to oxycodone hydrochloride on milligram basis as oral analgesic (DHHS review document; Gutstein and Akil, 2006). Similarly oral hydrocodone bitartrate has been shown to be approximately equipotent to or slightly less potent than oxycodone hydrochloride on milligram basis in producing abuse liability related subjective effects profile (Walsh et al., 2008). Therefore, ARCOS distribution data (for above mentioned drug salt forms) in kilogram quantities (without adopting any conversion factors to account for drug-specific potency differences) were used for calculating rates for these drugs. The results of these analyses are presented in the current review document. This expanded analysis showed that the hydrocodone combination products have high potential for abuse similar to that of schedule II opioid

analgesics.

1.2.3. Abuse of hydrocodone combination products in amounts sufficient to cause health hazards

Individuals are taking hydrocodone combination products in amounts sufficient to create a hazard to their health.

1.2.3.1. Poison control centers data

The National Poison Data System (NPDS), formerly known as Toxic Exposure Surveillance System (TESS), data are compiled by the American Association of Poison Control Centers (AAPCC) in cooperation with the majority of the United States poison centers. According to the annual reports of NPDS for the past several years, the number of hydrocodone toxic exposures and associated deaths were the largest followed by oxycodone among opioid analgesic drugs (Watson *et al.*, 2003, 2004, 2005; Lai *et al.*, 2006; Bronstein *et al.*, 2007). Table 6 provides annual toxic exposures mentioning hydrocodone and oxycodone and associated deaths from 2002 through 2006. Total annual toxic exposures and associated deaths involving hydrocodone combination products consistently exceeded those for oxycodone products. Majority of exposures were of intentional reason for both drugs.

Table 6. Annual toxic exposures involving hydrocodone and oxycodone (NPDS)§

Year	Hydrocodone		Oxycodone		Total for All Reported Substances	
	Exposures	Fatalities	Exposures	Fatalities	Exposures	Fatalities
2002	17,429	66	10,515	63	2,380,028	1,153
2003	19,578	82	11,254	60	2,395,582	1,106
2004	22,654	86	12,603	61	2,438,644	1,183
2005	22,229	100	13,191	78	2,424,180	1,261
2006*	22,244	105	13,473	91	2,403,539	1,229

*Changes in reporting were implemented in 2006.
§In the U.S., nearly 100 percent (of total kilogram amounts distributed) of hydrocodone was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone was marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

The rates of toxic exposures for oxycodone products calculated as the annual exposures per each 1 million prescriptions (Table 2) are substantially higher (up to 2-fold) as compared to the corresponding exposures for hydrocodone combination products from 2002 through 2006. However, when primary variable (average days of therapy per prescription) was accounted for as is the case with the use of total patient-days of therapy (Table 4) as the denominator, the rates of toxic exposures for hydrocodone combination products were similar to those for oxycodone products (Figure 1). Further, when both primary and majority of secondary variables were accounted for as is the case with the use of drug distribution data (as reported in ARCOS database, Table 5) as the denominator, the rates (per each 100 kilograms of drug) of toxic

exposures for hydrocodone combination products were higher compared to the corresponding rates for oxycodone products from 2002 through 2006 (Figure 2).

Smith *et al.* (2007) analyzed intentional exposures reports from poison control centers (7 or 15) for seven opioids at the 3-digit ZIP code level and calculated exposure rates on a quarterly basis using population or patient based denominators. Hydrocodone products had the largest

Figure 1. Drug Toxic Exposures/1 Million Patient-Days of Therapy

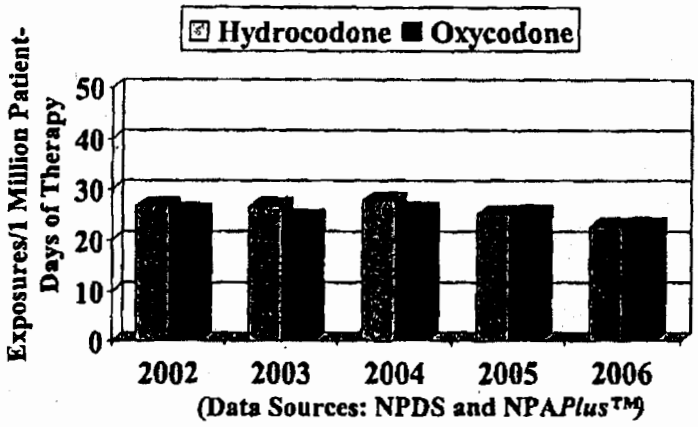
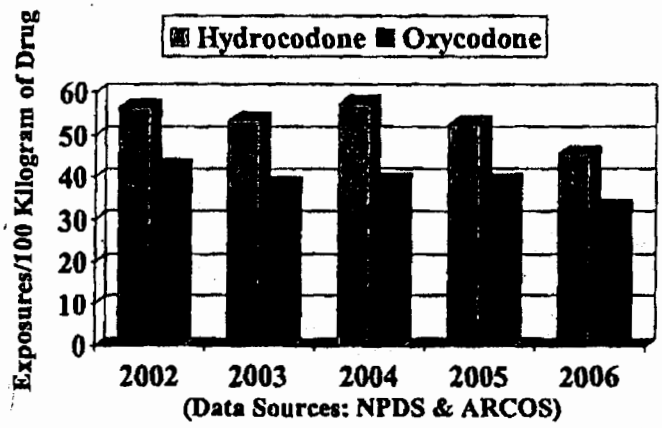


Figure 2. Drug Toxic Exposures/100 Kilograms of Drug in Salt Form



intentional exposure case load and was the most widely prescribed, while other oxycodone (combination and single-entity immediate-release products excluding single-entity extended-release products) products were the distant second in this regard. According to NPA*Plus*™, about 83 through 89% of total prescriptions for other oxycodone products (as defined in this publication) comprised of combination products. The aggregate population based exposure rate was the highest for hydrocodone products followed by other oxycodone products. In contrast, when exposure rates were calculated using the number of patients prescribed as the denominator, hydrocodone and other oxycodone products had the lowest rates, while methadone had the highest rates. These authors reasoned that population-based rates describe the health related burden of abuse or misuse of a given opioid on the population as a whole, thus places it in the

comparative context with other public health problems. In contrast, patient-based rates provide the burden of abuse and misuse of a given opioid relative to the degree of benefit it offers to patients and thus it provides drug-specific risk-benefit profile. Based on this reasoning, similar patient-based exposure rate for hydrocodone combination products versus other oxycodone products (majority of these are oxycodone combination products) as reported by these authors suggest these two types of products had similar abuse risk relative to their medical benefits.

1.2.3.2. Drug Abuse Warning Network (DAWN) emergency department data

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug abuse related emergency department (ED) visits and deaths. As mentioned in detail in the DHHS review document, there were major changes in reporting of data in 2003. Thus the data prior to 2003 can not be trended with the data for recent years. Thus the data for pre- and post-2003 data are presented separately.

1.2.3.2.1. DAWN emergency department data for 2002 and prior years

The methodological details for DAWN data collection prior to and for the year 2002 are presented below. The data is collected from a representative sample of eligible hospitals (non-Federal, short stay, general medical and surgical hospitals that operate EDs that are open 24 hours a day, 7 days a week) located throughout the coterminous U.S., with oversampling in 21 metropolitan areas and a National Panel of hospitals sampled from locations outside these areas. In 2002, the DAWN sample consisted of 549 eligible hospitals. Of these 437 (80%) participated in DAWN. Response rates in the 21 metropolitan areas ranged from 65% to 100%, with 7 metropolitan areas having response rates below 75%. Upon computing estimates for 21 metropolitan areas and for National Panel of hospitals, these data are pooled to calculate estimates for coterminous U.S. The patient presenting to the ED must meet all of the following criteria for inclusion in the DAWN reports:

- The patient was age 6 to 97;
- The patient was treated in the hospital's ED;
- The patient's presenting problem(s) (i.e., the reason for the ED visit) was induced by or related to drug use, regardless of when the drug use occurred;
- The episode involved the use of an illegal drug, or the use of a legal drug or other chemical substance for non-medical purposes; and
- The patient's reason for using the substance(s) was dependence, suicide attempt or gesture, and/or psychic effect.

A reported ED visit that involved drug abuse was defined as drug abuse episode. A single drug abuse episode may have multiple drug mentions (up to 4 different substances). The number of ED episodes reported to DAWN is not equivalent to the number of individual patients, because one person may make repeated visits to an ED. DAWN contain no individual identifiers. Table 7 lists the estimated number of emergency department (ED) mentions involving hydrocodone and oxycodone for 1994 through 2002. Annual mentions of ED visits for hydrocodone consistently exceeded those for oxycodone during this period.

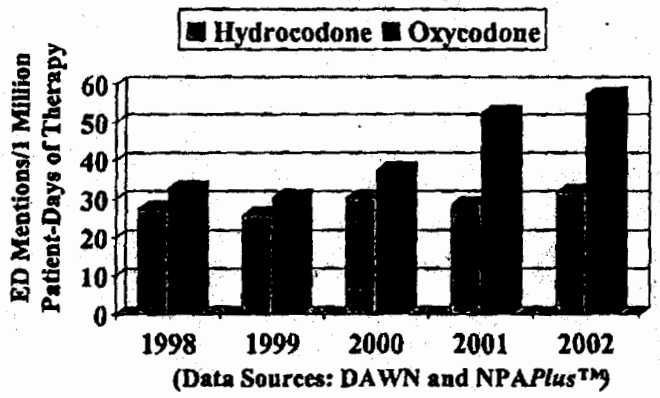
Table 7. ED Mentions (DAWN) and total prescriptions (NPA*Plus*™, formerly known as IMS Health, Inc) for hydrocodone combination products and oxycodone products§

Year	Hydrocodone		Oxycodone	
	ED Mentions	Total Prescriptions (in thousands)	ED Mentions	Total Prescriptions (in thousands)
1994	9,320		4,069	
1995	9,686		3,393	
1996	11,419		3,190	
1997	11,570		5,012	
1998	13,611	71019.84	5,211	16183.39
1999	15,252	81725.17	6,429	19225.1
2000	20,098	88778.49	10,825	23312.4
2001	21,567	96318.03	18,409	26513.06
2002	25,197	103645.3	22,397	29296.44

§In the U.S., nearly 100 percent (of total kilogram amounts distributed) of hydrocodone was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone was marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

The rates of ED mentions, for oxycodone products calculated as the number of annual ED mentions per each 1 million prescriptions (Table 2) are substantially higher (up to 3-fold) as compared to the corresponding ED mentions for hydrocodone combination products from 1998 through 2002. However, when primary variable (average days of therapy per prescription) was accounted for as is the case with the use of total patient-days of therapy (Table 4) as the denominator, the differences in the rates of ED mentions for hydrocodone combination products versus oxycodone products were reduced (Figure 3). Further, when both primary and majority of secondary variables were accounted for as is the case with the use of drug distribution data (as reported in ARCOS database, Table 5) in kilogram quantities as the denominator, the rates (per each kilogram of drug distributed) of ED mentions for hydrocodone combination products are

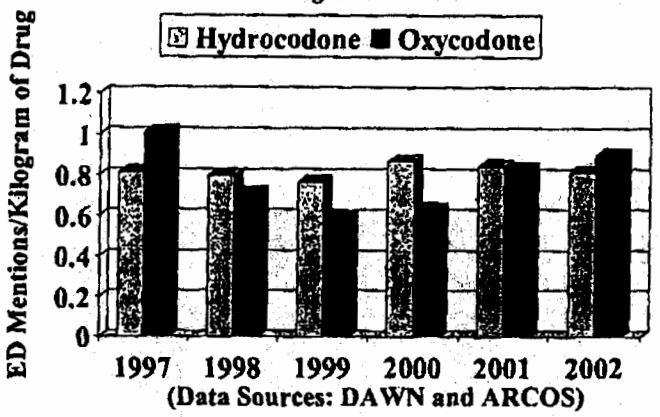
Figure 3. Emergency Department Mentions/1 Million Patient-Days of Therapy



(Data Sources: DAWN and NPA*Plus*™)

similar to those for oxycodone products from 1998 through 2002 (Figure 4). These data suggest that both share similar potential to cause abuse-related ED visits.

Figure 4. Emergency Department Mentions/Kilogram of Drug in Salt Form



Further these data also do not support the supposition that the nonnarcotic active ingredients present in hydrocodone combination products reduce the abuse potential of hydrocodone. For example, because nearly 100% (of kilogram amounts) of hydrocodone was distributed (sold) as its combination products, while only 24 through 28% (of kilogram amounts) of oxycodone was sold as combination products, the above supposition predicts that hydrocodone combinations products on kilogram basis would cause abuse related ED visits at rates lower than those for oxycodone products. Contrary to this prediction, the present data using ARCOS distribution data as denominator indicate that hydrocodone products on kilogram basis cause abuse related ED visits at rates similar to those for oxycodone products. This shows that the hydrocodone combination products are similar to oxycodone products in their potential for abuse. Thus these data indicate that nonnarcotic active ingredients present in hydrocodone combination products do not reduce the abuse potential of hydrocodone.

1.2.3.2.2. DAWN data for 2004, 2005 and 2006

The DAWN data for 2003 was not reported for full year. Annual DAWN data for national estimates for ED mentions for 2004, 2005 and 2006 was published. ED mentions for hydrocodone in 2004, 2005, and 2006 were 37,844, 47,192 and 57,550, respectively. The corresponding numbers for oxycodone were 41,701, 52,943 and 64,888, respectively. .

The rates of ED mentions in 2004, 2005 and 2006 for oxycodone products, calculated as the number of annual ED mentions per each 1 million prescriptions (Table 2), are substantially higher (about 3.5-fold) as compared to the corresponding ED mentions for hydrocodone combination products. However, when primary variable (average days of therapy per prescription) was accounted for as is the case with the use of total patient-days of therapy (Table 4) as the denominator, the differences in the rates of ED mentions for hydrocodone combination products and oxycodone products were reduced (about 2 to 2.5 fold) (Figure 5). Further, when both primary and majority of secondary variables were accounted for as is the case with the use

of drug distribution data (as reported in ARCOS database, Table 5) in kilogram quantities as the denominator, the rates (per each kilogram of drug distributed) of ED mentions for hydrocodone combination products are slightly higher (about 1.28 to 1.38-fold) higher than those for oxycodone products (Figure 6). These findings from new DAWN database is consistent with those obtained using previous DAWN database (2002 and prior years).

Figure 5. Emergency Department Mentions/1 Million Patient-Days of Therapy

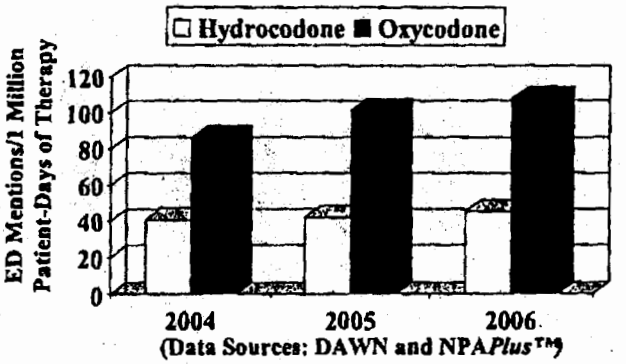
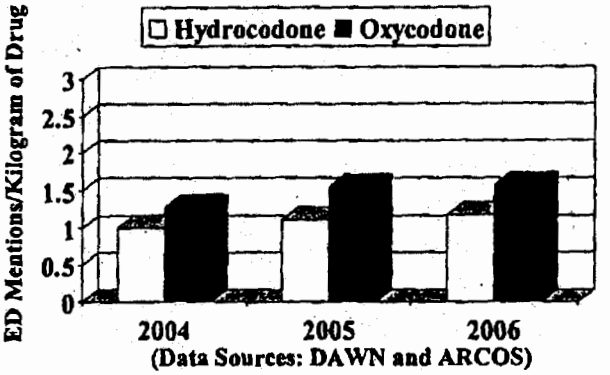


Figure 6. Emergency Department Mentions/Kilogram of Drug in Salt Form



The above findings from the data analysis using ARCOS drug distribution data as a denominator are consistent with those reported by Dasgupta et al. (2006). These authors used retail drug distribution amounts (as reported by IMS Health's National Prescription Audit) as a denominator and found that number of opioid analgesics including hydrocodone and oxycodone, when adjusted for relative potency differences, had similar annual morbidity rates, calculated as the number of ED mentions (as reported in DAWN) per each kilogram (as reported in IMS Health's National Prescription Audit) of drug dispensed from 1994 through 2002. These authors reasoned that a constant fraction of each opioid including hydrocodone and oxycodone is being diverted to the illicit market. Contrary to these and DEA's present findings, DHHS using total prescriptions as denominator to calculate annual morbidity rates found that the rates for hydrocodone are lower than that for oxycodone. As discussed earlier in this section, this discrepancy may be due to the fact that the use of total prescriptions does not take into account drug-specific differences with regard to the average days of therapy per prescription, dosage units per prescription, the strength of the product, and the composition (single-entity versus combination products) and formulation types (immediate-release versus extended-release

products).

DHHS further found that annual morbidity rates, calculated as the number of ED mentions relative to the total prescriptions dispensed, for hydrocodone increased from 18 per 100,000 prescriptions in 1997 to 24 per 100,000 prescriptions in 2002, while these for oxycodone increased at steeper rates from 35 in 1997 to 76 in 2002. The only major category of illegal drug use to have risen since 2002, prescription drug abuse poses a particular challenge. Prescription drug abuse has emerged as a new drug threat that requires a concerted response from every sector of our society. Abuse of opioid analgesics is of particular concern, because of the large number of users, the high addictive potential, and the potential to induce overdose or death (National Drug Control Strategy, 2008, the White House). However, it is important to note that such steep increase could be due to other variable such as introduction of a high strength extended-release product (e.g., OxyContin®) approved for marketing during this period and the subsequent increase in its popularity among prescription opioid abusers.

Further, as discussed earlier in this section, DEA determined that the use of prescriptions is not an appropriate denominator for these calculations. For example it does not take into account of the fact that oxycodone products, besides as combinations products, are marketed as high strength single-entity extended-release products. As mentioned earlier in this section, the average drug amount per dosage unit of oxycodone single-entity products (over 23 mg per each dosage unit) far exceeds that present in oxycodone combination products (over 6 mg per each dosage unit) and hydrocodone combination products (over 7 mg per each dosage unit). This fact is of particular significance in determining the potential of a given drug to make individuals seek admissions to hospitals due to its abuse related adverse health effects. Therefore, for the present evaluation, DEA used two additional denominators namely total patient-days of therapy and total kilogram amounts of drug distributed to calculate annual rates of ED mentions.

In summary, DAWN data demonstrate that abuse of hydrocodone combination products, similar to oxycodone products, has been escalating. The rates of abuse as represented by the number of ED mentions per each kilogram of hydrocodone distributed in the U.S. are similar (during 1997 through 2002) or slightly smaller (during 2004 through 2006) than those for oxycodone. The nonnarcotic active ingredients present in hydrocodone combination products do not reduce the abuse potential of hydrocodone.

1.2.3.3. Florida Department of Law Enforcement (FDLE) medical examiners data

According to annual reports of the Florida Department of Law Enforcement (FDLE), in 2007, there were 8,620 drug-related deaths (whether implicated as the cause of death or mentioned as merely present) in Florida. FDLE mentioned both hydrocodone and oxycodone among the list of drugs that caused most deaths in 2006. Hydrocodone and oxycodone mentions for 2007 increased by 10.4% and 35.8%, respectively as compared to the corresponding data for 2006 (Table 8). ARCOS reported that the amount of hydrocodone (as salt form) distributed to Florida decreased by 6.4% from 3,752.17 kilograms in 2006 to 3,511.79 kilograms in 2007, while the amount of oxycodone (as salt form) distributed increased by 47.4% from 4,398.66 kilograms in 2006 to 6,482.97 kilograms in 2007 (Table 9). Total prescriptions and total patient-days of therapy for hydrocodone are larger than those for oxycodone (Table 9).

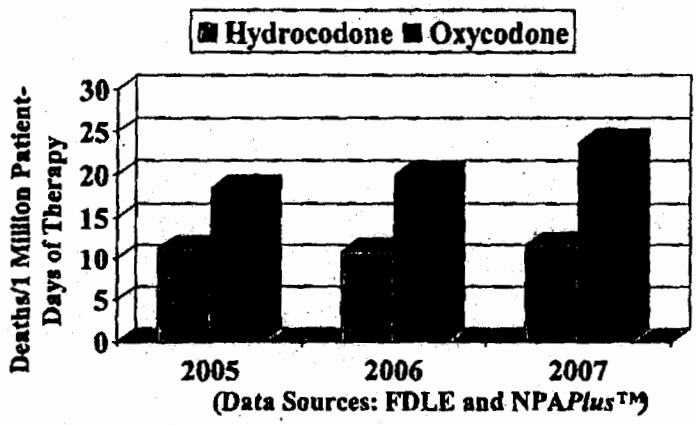
Table 8. Hydrocodone and oxycodone related deaths in Florida (FDLE)§

	Hydrocodone			Oxycodone		
	As cause of death	Mentioned, but not implicated as cause of death	Total drug associated deaths	As cause of death	Mentioned, but not implicated as cause of death	Total drug associated deaths
2005	221	427	648	340	376	716
2006	236	495	731	496	427	923
2007	264	543	807	705	548	1,253

§In the U.S., nearly 100 percent (of total kilogram amounts distributed) of hydrocodone was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone was marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

In Florida, total annual deaths associated with oxycodone products exceeded those for hydrocodone combination products in recent years (Table 8). The rates of drug associated deaths per each 1 million prescriptions (Table 9) for oxycodone products were substantially higher (up to 3-fold) than those for hydrocodone combination products from 2005 through 2007. However, when primary variable (average days of therapy per prescription) was accounted for as is the case with the use of total patient-days of therapy (Table 9) as the denominator, the differences in the rates of deaths associated with hydrocodone combination products versus oxycodone products were reduced (Figure 7). Further, when both primary and majority of secondary variables were accounted for as is the case with the use of drug distribution data (in kilograms) in Florida (as reported in ARCOS database, Table 9) as the denominator, the rates of deaths associated with each 100 kg of drug distributed in Florida for these two drugs are similar (Figure 8). These data on drug-associated death rates indicate that both hydrocodone and oxycodone on a kilogram basis have approximately similar rates of mortality.

Figure 7. Drug-Associated Deaths in Florida/1 Million Patient-Days of Therapy*



*Total patient-days of therapy were calculated using National average days of therapy per prescription for these drugs

Figure 8. Drug-Associated Deaths in Florida/100 Kilograms of Drug in Salt Form

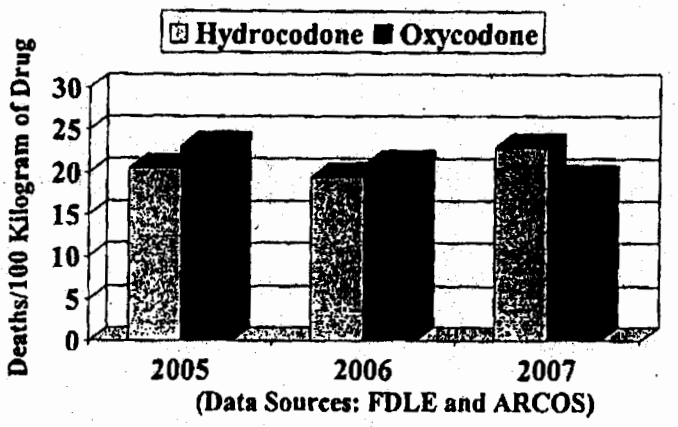


Table 9. Annual total prescriptions (NPA*Plus*™) and total patient-days of therapy (calculated from using national average days of therapy obtained from NPA*Plus*™) and annual drug amounts distributed (kilograms in salt form as reported in ARCOS[Φ]) for hydrocodone and oxycodone in Florida from 2005 through 2007 [§]

Drug	Data System	Parameter	2005	2006	2007
Hydrocodone	ARCOS	Drug Amount Distributed (Kg in salt form)	3,253.38	3,752.17	3,511.79
	NPA*Plus*™	Total Prescriptions	6,336,872	6,854,545	6,895,564
		Total Patient-Days of Therapy	57,947,794	67,431,286	69,680,072
Oxycodone	ARCOS	Drug Amount Distributed (Kg in salt form)	3,118.45	4,398.66	6,482.97
	NPA*Plus*™	Total Prescriptions	2,825,174	3,267,846	3,573,258
		Total Patient-Days of Therapy	38,913,020	46,383,409	52,883,377

ΦThe vast majority of oxycodone products are formulated in the hydrochloride salt form while hydrocodone combination products are primarily formulated in the bitartrate salt. Thus the molecular weights of these two salt forms were used for conversion from the base to the corresponding salt form.
§In the U.S., nearly 100 percent (of total kilogram amounts distributed) of hydrocodone was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone was marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

FDLE also reported information about the drug being the "cause" of death or merely "present" in the body at the time of death. Mentions of oxycodone as cause of deaths were substantially larger than those for hydrocodone. In contrast, with regard to the deaths in which drug was mentioned as present, but not implicated as cause of death, hydrocodone had consistently larger, though small in magnitude, numbers of mentions than those for oxycodone. These differential patterns between hydrocodone and oxycodone may possibly be due to

pharmaceutical formulation differences. For example, oxycodone, besides combination products (typically up to a maximum of 10 mg of oxycodone), is also marketed as moderate strength single-entity immediate-release products (up to 30 mg per dose unit) and high strength extended-release products (up to 80 mg per dose unit), while hydrocodone is marketed only as low strength (typically up to 10 mg hydrocodone per each dose unit) combination products. Thus, because of high drug amount present in each dosage unit of high strength extended-release oxycodone products, such products of oxycodone are more likely to be mentioned as cause of deaths than hydrocodone products.

1.2.4. Diversion of hydrocodone combination products

There is a significant diversion of hydrocodone combination products from legitimate drug channels.

1.2.4.1. Forensic laboratory data

The data from the National Forensic Laboratory Information System (NFLIS) and the System to Retrieve Information from Drug Evidence (STRIDE) are presented in Table 10. The NFLIS is a laboratory data collection system of state and local forensic laboratories throughout the United States. The STRIDE database contains information on drug exhibits analyzed in the DEA forensic laboratory system that have been submitted to the laboratory as drug evidence from seizures and undercover purchases.

Table 10. Total cases and drug exhibits reported in NFLIS (Data retrieved on March 14, 2008) and STRIDE (data retrieved on March 21, 2008)§

Year	Hydrocodone				Oxycodone			
	NFLIS		STRIDE		NFLIS		STRIDE	
	Cases	Exhibits	Cases	Exhibits	Cases	Exhibits	Cases	Exhibits
1996			56	139			33	60
1997			56	187			36	70
1998			59	103			38	51
1999			98	235			66	125
2000			105	259			75	218
2001			134	315			176	522
2002	8934	10174	172	337	7807	9035	186	429
2003	11429	13179	188	520	9235	10788	196	523
2004	15497	17741	202	534	12682	14979	227	514
2005	19523	22517	243	598	13490	16273	241	656
2006	22947	26439	255	659	16562	20114	254	645
2007	25034	29447	241	732	18709	22782	261	702

§In the U.S., nearly 100 percent (of total kilogram amounts distributed) of hydrocodone was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone was marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

Because NFLIS and STRIDE are law enforcement databases, the data as presented in this document contain information from both spontaneous encounters as well as targeted priority based investigations. The cases reported in the STRIDE database contain information about the actual drug amounts as well as the drug form. However, the STRIDE database does not always list the actual or suspected dosage strengths. As a consequence, no differentiation can be made as to the actual dose of each tablet, capsule or liquid that was seized and analyzed. Unlike, STRIDE, the NFLIS does not consistently report the actual drug amounts in each case. Further, NFLIS data cannot be used for 'trending' analyses since new labs were added each year. For the years 2003 and 2004, data was collected from forensic laboratories that handled over 70% of all state and local drug analysis cases in the U.S. Since 2005, data was collected from forensic laboratories that handled over 88% of all state and local drug analysis cases in the U.S.

According to NFLIS, since 2002, both hydrocodone and oxycodone have been consistently reported as among the top 10 most frequently encountered drugs. Hydrocodone followed by oxycodone are the leading diverted controlled pharmaceuticals among opioid analgesic drugs. Similar to NFLIS, STRIDE has also consistently reported that hydrocodone and oxycodone are the leading diverted controlled pharmaceuticals among the opioid analgesics drugs. Although cumulative total cases (1690) and exhibits (4607) for hydrocodone reported during 1996 through 2007 were similar to those for oxycodone (1656 cases and 4515 exhibits), the average units, especially solid dose forms comprising of tablets and capsules, per case basis were larger for hydrocodone than for oxycodone (Table 11). For example, average number of solid dosage units (tablets and capsules) per each hydrocodone case was 4-fold larger than that for oxycodone.

Table 11. Cumulative total amounts of drug exhibits for hydrocodone and oxycodone reported by STRIDE from 1996 through 2007 (data retrieved on March 21, 2008) §

Measure	Hydrocodone			Oxycodone		
	Solid Dosage Units (Tablets or Capsules)	Powder (Grams)	Liquid (milliliters)	Solid Dosage Units (Tablets or Capsules)	Powder (Grams)	Liquid (milliliters)
Totals	2,031,465	18,027	115,884	490,828	6390	1900
Average /Case*	***1,202***	10.67	68.57	***296***	3.86	1.147

*Averages per case basis was calculated by using the total number of cases recorded. During 1996 to 2007, there were a total 1,690 cases involving 4,607 hydrocodone drug exhibits. The corresponding numbers for oxycodone were 1,656 cases and 4,515 oxycodone drug exhibits.

§In the U.S., nearly 100 percent (of total kilogram amounts distributed) of hydrocodone was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone was marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

Figure 9. Cases/1 Million Patient-Days of Therapy

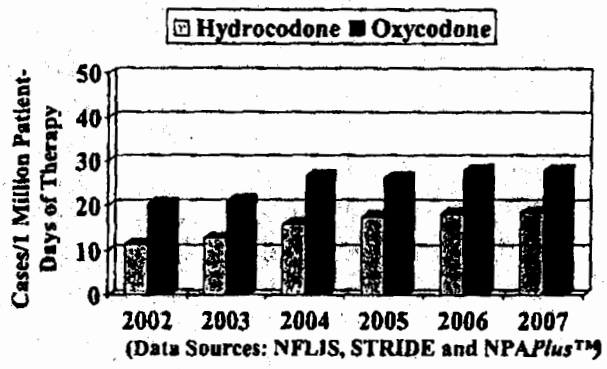
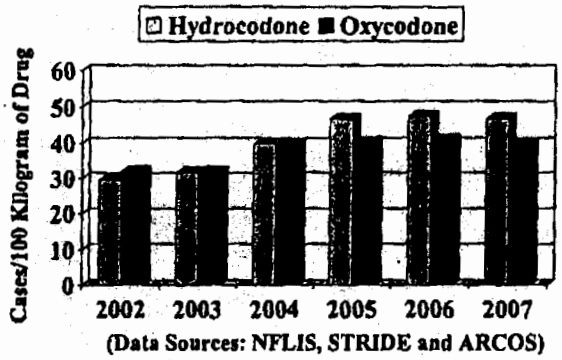
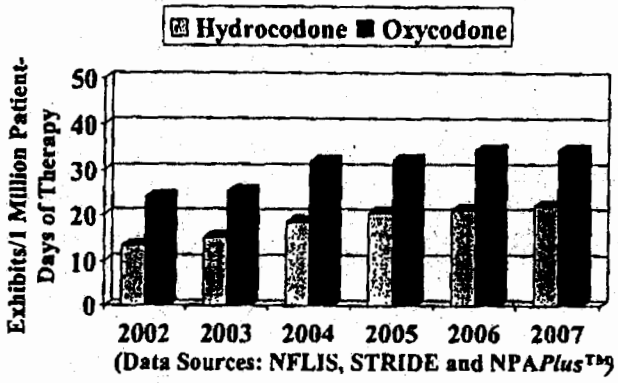


Figure 10. Cases/100 Kilograms of Drug in Salt Form



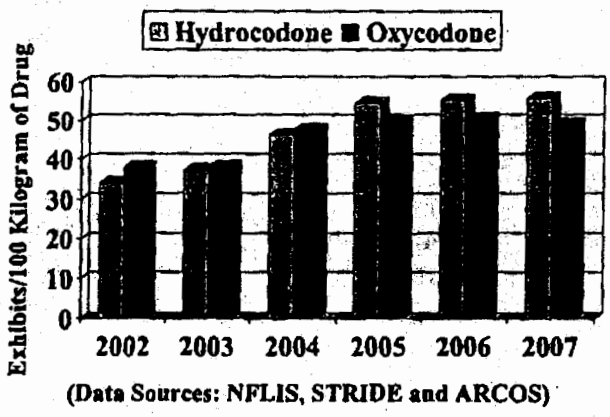
Although the above data illustrate the high degree of illicit trafficking and diversion of hydrocodone and oxycodone, the rates of diversion of these drugs in reference to their respective total availability in the market is a useful parameter in evaluating their relative abuse potentials. DHHS used total prescriptions as a denominator to indicate drug availability. For the reasons as discussed earlier, DEA used two additional denominators namely total patient-days of therapy and drug distribution (sales) data from ARCOS database for calculating these rates and are presented in the current review document. The rates of diversion of oxycodone products as indicated by the annual forensic cases or exhibits (NFLIS + STRIDE) per each 1 million prescriptions (Table 2) are substantially higher (up to 3-fold) as compared to the corresponding rates for hydrocodone combination products from 2002 through 2007. However, when the primary variable (average days of therapy per prescription) was accounted for as is the case with the use of total patient-days of therapy (Table 4) as the denominator, the differences in the number of cases or exhibits per million patient-days of therapy between hydrocodone combination products versus oxycodone products were substantially reduced (Figures 9 and 11).

Figure 11. Exhibits/1 Million Patient-Days of Therapy



Further, when both primary (average days of therapy per prescription) and majority of secondary variables (drug-specific differences in composition, formulation, strength and dosage units per prescription) were accounted for, as is the case with the use of ARCOS drug distribution data as the denominator, the rates of diversion of hydrocodone combination products as indicated by the annual forensic cases or exhibits (NFLIS+STRIDE) per each 100 kg of drug distributed (Table 5) are similar or slightly higher compared to the corresponding rates for oxycodone products from 2002 through 2007 (Figures 10 and 12).

Figure 12. Exhibits/100 Kilograms of Drug in Salt Form



The above mentioned expanded data analysis do not support the supposition that the nonnarcotic active ingredients present in hydrocodone combination products reduce the abuse potential of hydrocodone. For example, because nearly 100% (of kilogram amounts) of hydrocodone was distributed (sold) as its combination products, while only 24 through 28% (of kilogram amounts) of oxycodone was sold as combination products, the supposition predicts that hydrocodone combinations products on kilogram basis would be diverted and abused at rates lower than oxycodone products. Contrary to this prediction, the present data using ARCOS distribution data as denominator indicate that hydrocodone products on kilogram basis are diverted at rates similar to or slightly larger than those of oxycodone products.

In summary, forensic laboratory data (NFLIS and STRIDE) indicate that hydrocodone and oxycodone products are trafficked and diverted. These are the leading diverted controlled pharmaceuticals among opioid analgesic drugs. When primary and majority of secondary variables are accounted for, hydrocodone combination products are diverted at rates that are equal to or slightly larger than the corresponding rates for oxycodone products. These data also indicate that the nonnarcotic active ingredients that are present in hydrocodone combination products do not reduce its diversion potential.

1.2.4.2. Diversion from Internet pharmacies

The non-medical use of controlled pharmaceuticals has been exacerbated by rogue Internet pharmacies in recent years. Recent General Accounting Office investigated the availability of hydrocodone products through Internet without a prescription and reached the following conclusion (GAO-04-892T, 2004).

"Our investigation revealed that customers can purchase hydrocodone, a potentially dangerous and addictive controlled substance, from certain domestic Internet sites that do not require prescriptions. These Web sites appear to purposely cater to hydrocodone customers who are willing to pay a substantial markup for the painkillers because they do not have prescriptions. As a result, these sites appear to be in the business of profiting from illicit drug use rather than providing a safe, inexpensive alternative source of drugs for customers."

DEA investigations reveal that the nonmedical use of controlled pharmaceuticals, specifically hydrocodone, alprazolam and phentermine, has been exacerbated by Internet websites that solicit drug orders from individuals. The operators of these websites (i.e. rogue Internet pharmacies) often collaborate, either directly or indirectly, with DEA-registered brick and mortar pharmacies that either exclusively fill Internet prescriptions or as a percentage of their business service walk in customers as well. Table 12 provides ARCOS data for the distribution of controlled opioid analgesics to the 71 pharmacies (identified by DEA) that are suspected to have engaged either directly or indirectly with rogue Internet pharmacies from 2005 through 2007. These data represent amounts ordered and shipped to these 71 pharmacies from distributors. These data are presented both in absolute amounts (gm) and as morphine equivalent amounts.

The above mentioned 71 pharmacies ordered a cumulative total of 1,041.3 kg of hydrocodone from 2005 through 2007 that are markedly larger than the corresponding average amounts ordered by all pharmacies in the U.S (Table 13). Average amounts of hydrocodone combination products ordered by these 71 pharmacies are about 12-, 16- and 5- fold larger than their corresponding average amounts distributed to all pharmacies in the U.S. in 2005, 2006 and 2007, respectively. However, these 71 pharmacies, as compared to average amounts ordered by all pharmacies in the U.S., did not order other schedule II and schedule III opioid products in a manner that is similar in magnitude to that of hydrocodone combination products. The differences between the above mentioned 71 pharmacies and all U.S. pharmacies with regard to the total annual amounts of other opioid products ordered were smaller than the corresponding differences for hydrocodone combination products ordered.

Table 12. Opioid analgesic drug sales (in grams) to 71 pharmacies (identified by DEA) suspected to have filled illegal Internet prescriptions (ARCOS) *

Narcotics	2005		2006		2007	
	Amounts	Amounts in Morphine equivalentsΦ	Amounts	Amounts in Morphine equivalentsΦ	Amounts	Amounts in Morphine equivalentsΦ
Hydrocodone	343,732 (74%)	687,464 (77%)	510,932 (77%)	1,021,864 (80.7%)	186,645 (54%)	373,290 (56.1%)
Oxycodone	51,777 (11.2%)	103,554 (11.6%)	66,938 (10%)	133,876 (10.6%)	96,574 (28%)	193,148 (29.0%)
Codeine	30,209 (6.5%)	11,479 (1.3%)	38,041 (6%)	14,456 (1.1%)	23,190 (6.7%)	8,812 (1.3%)
Morphine	13,924 (3.0%)	13,924 (1.6%)	16,663 (2.5%)	16,663 (1.3%)	14,574 (4.2%)	14,574 (2.2%)
Methadone	11,370 (2.5%)	34,110 (3.8%)	11,834 (1.8%)	35,502 (2.8%)	13,981 (4%)	41,943 (6.3%)
Buprenorphine	893 (<1%)	22,325 (2.5%)	1,021 (<1%)	25,525 (2.0%)	519 (<1%)	12,975 (2%)
Fentanyl	357 (<1%)	8,925 (1%)	362 (<1%)	9,050 (0.7%)	339 (<1%)	8,475 (1.3%)
Hydromorphone	884 (<1%)	7,072 (0.8%)	965 (<1%)	7,720 (0.6%)	931 (<1%)	7,448 (1.1%)
Oxymorphone	-		54 (<1%)	540 (<1%)	346 (<1%)	3,460 (<1%)
Meperidine	1,802 (<1%)	360 (<1%)	1,922 (<1%)	384 (<1%)	3,481 (1%)	696 (<1%)
Dihydrocodeine	28.4 (<1%)	28.4 (<1%)	13 (<1%)	13 (<1%)	34 (<1%)	34 (<1%)
Opium Powder	18 (<1%)		8 (<1%)		6 (<1%)	
Levorphanol	1.1 (<1%)	16.5 (<1%)	1.2 (<1%)	18 (<1%)	1.6 (<1%)	24 (<1%)

* Data expressed in grams for base forms of these drugs. Numerals in parentheses indicate amount as the percent of all controlled substances.

ΦMorphine equivalents were calculated using potencies of opioid analgesics relative morphine. The relative potencies for majority of opioid analgesics mentioned in this table, with the exception of buprenorphine, levorphanol and dihydrocodeine, were taken from those reported by Dasgupta *et al.* (2006). These relative potencies for hydrocodone, oxycodone, codeine, methadone, meperidine, hydromorphone, and fentanyl were 2, 2, 0.38, 3, 0.2, 8, and 25, respectively. Relative potencies for buprenorphine (25), levorphanol (15) and oxymorphone (10) were derived based on equianalgesic doses mentioned by Gutstein and Akil (2006). Dihydrocodeine was considered equipotent to morphine based on oral dose formulations available in the market.

Table 13. Comparison of average amounts (grams) of opioid analgesics distributed to 71 pharmacies (identified by DEA) suspected to have filled illegal Internet prescriptions versus average amounts distributed to all pharmacies in the U.S. (ARCOS) *

Drug	2005			2006			2007		
	U.S. Pharmacy Average	Rogue Internet Pharmacy Average		U.S. Pharmacy Average	Rogue Internet Pharmacy Average		U.S. Pharmacy Average	Rogue Internet Pharmacy Average	
	Grams	Grams	*% of U.S. Pharmacy Average*	Grams	Grams	*% of U.S. Pharmacy Average*	Grams	Grams	*% of U.S. Pharmacy Average*
Hydrocodone	398.82	4841.3	*1,214%*	454.7	7196.2	*1,583%*	496.8	2628.8	*529%*
Oxycodone	488.55	729.2	*149%*	585.6	942.8	*161%*	673.0	1360.2	*202%*
Codeine	284.26	425.4	*150%*	277.6	535.8	*193%*	271.3	326.6	120%
Morphine	222.83	196.1	*88%*	259.1	234.7	*91%*	274.3	205.3	75%
Methadone	100.28	160.1	*160%*	119.8	166.7	*139%*	126.8	196.9	155%
Buprenorphine	6.84	12.6	*184%*	9.4	14.4	*152%*	12.6	7.3	58%
Fentanyl	6.05	5.0	*83%*	6.6	5.1	*77%*	6.9	4.8	69%
Hydromorphone	13.55	12.4	*92%*	14.8	13.6	*92%*	15.9	13.1	82%

* Data expressed are gram amounts of drug in base form.

On January 22, 2007, DEA launched "Operation Lightning Strike," an initiative that targeted DEA registered pharmacies that allegedly were filling illegal controlled substance prescriptions obtained from by customers over numerous websites. By February 21, 2007, DEA had suspended all six targeted pharmacies and two additional pharmacies that were filling illegal Internet prescriptions for controlled substances. DEA removed 907,238 dosage units of hydrocodone combination products and bulk hydrocodone (equivalent to 600,000 ten-milligram dosage units). U.S. pharmacies on average purchase less than 8,000 dosage units of hydrocodone per month. Each suspended pharmacy possessed more than 21,000 dosage units of hydrocodone. The "Operation Lightning Strike" resulted in shutting down of a total of ten pharmacies. These ten pharmacies alone purchased more than 35 million dosage units of hydrocodone in 2006, the vast majority of which were used to fill orders placed by customers illegally over the Internet.

1.2.5. Actual abuse data from drug abuse surveys

Drug abuse data from national surveys indicate that individuals are taking hydrocodone combination products on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs.

1.2.5.1. National Survey on Drug Use and Health (NSDUH)

The National Survey on Drug Use and Health (NSDUH), formerly the National Household Survey on Drug Use (NHSDA), provides annual data on drug abuse by the U.S. population age 12 or older of a number of illicit and prescription drugs. In 2006, about 32.7 million U.S. population aged 12 or older used pain relievers for non-medical purpose at least once in their lifetime. The estimated total number of non-medical users of pain relievers has also shown significant increases over the last few years of the survey (data prior to 2002 were not trendable because of major changes in the system). According to the NSDUH report (2007), the combined data from 2002 through 2005 indicate that 57.7 percent of persons who first used pain

relievers non-medically in the past year used hydrocodone products and 21.7 percent used oxycodone products.

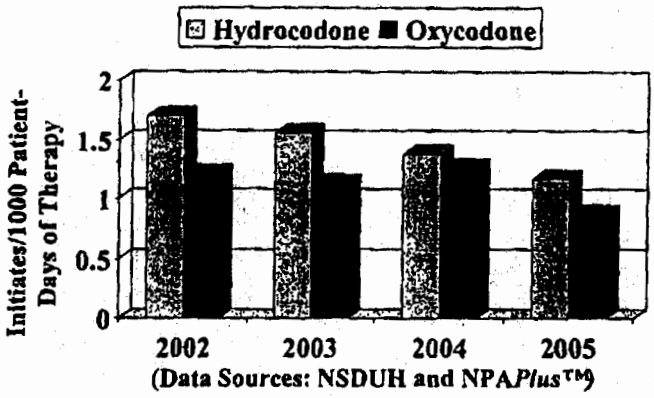
Annual reports of NSDUH in general do not contain pharmaceutical substance- and drug product-specific data. DHHS review document provided some drug-specific NSDUH data for hydrocodone and oxycodone for the years 2002 through 2005. These numbers were shown in the Table 14 and some of these data were used to calculate drug-specific abuse rates. These data show that lifetime users and past year initiates (defined as persons who used the substance for the first time in the 12 months prior to date of interview) of hydrocodone combination products were larger than those of oxycodone products. For example, in 2005, about 18.9 and 1.3 million individuals (12 years or older) were lifetime users and past year initiates for hydrocodone, respectively. The corresponding numbers for oxycodone were 12.0 and 0.46 millions. According to the DHHS review, the lifetime users of hydrocodone for 2005 represented about 7.8 percent of total U.S. population age 12 years or older. The corresponding rate for oxycodone was 4.9 percent. These data indicate that these pharmaceutical products have become popular drugs of abuse among U.S. population age 12 or older.

Table 14. Non-medical use of hydrocodone combination products and oxycodone products[§]

Drug	Data Type	Numbers in Thousands			
		2002	2003	2004	2005
Hydrocodone[1]	Lifetime Users	13,952	16,808	17,734	18,875
	Past Year Initiates	1,349	1,403	1,352	1,314
Oxycodone[2]	Lifetime Users	10,151	11,538	11,925	12,029
	Past Year Initiates	474	503	608	455

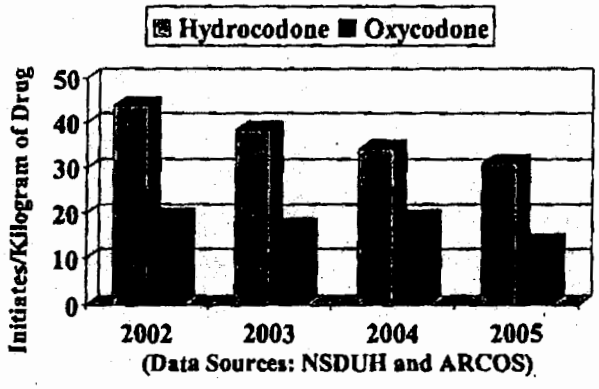
[1]Includes Vicodin®, Lortab®, or Lorcet, ® and generic hydrocodone and other pain relievers containing hydrocodone that respondents specified.
[2]Includes Percocet®, Percodan®, or Tylox® and OxyContin® and other pain relievers containing oxycodone that respondents specified.
§In the U.S., nearly 100 percent (of total kilogram amounts distributed) of hydrocodone was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone was marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

Figure 13. Past Year Initiates/1000 Patient-Days of Therapy



The rates of past year initiates, calculated as the number of past year initiates per each 1 million prescriptions (Table 2), for oxycodone products are slightly higher (up to about 1.5-fold) as compared to the corresponding rates for hydrocodone combination products from 2002 through 2005. However, when primary variable (average days of therapy per prescription) was accounted for as is the case with the use of total patient-days of therapy (Table 4) as the denominator, the differences in the rates of past year initiates for hydrocodone combination products and oxycodone products were eliminated with a slight reversal trend (Figure 13). Further, when both primary and majority of secondary variables were accounted for as is the case with the use of drug distribution data (as reported in ARCOS database, Table 5) as the denominator, the rates (per each 1 kilogram of drug) of past year initiates for hydrocodone combination products were substantially higher compared to the corresponding rates for oxycodone products from 2002 through 2005 (Figure 14).

Figure 14. Past Year Initiates/Kilogram of Drug in Salt Form



For the reasons explained below, these data do not support the supposition that the nonnarcotic active ingredients that are present in hydrocodone combination products reduce the abuse potential of hydrocodone. Nearly 100% (of kilogram amounts) of hydrocodone was distributed (sold) as its combination products, while only 24 through 28% (of kilogram amounts) of oxycodone was sold as combination products. Therefore if the supposition that nonnarcotic ingredients present in hydrocodone products deter their abuse were to be true, this would result in substantially lower rates of abuse for hydrocodone combination products than that of oxycodone products. Contrary to this prediction, the present analysis using ARCOS distribution

data as a denominator indicate that hydrocodone combination products on kilogram basis are abused (past year initiates) at rates substantially higher than those for oxycodone products. This suggests that the nonnarcotic active ingredients that are present in hydrocodone combination products do not mitigate the abuse potential of hydrocodone.

The NSDUH data provided by DHHS also indicate that the percentages of lifetime non-medical users of hydrocodone combination products reporting past year use of any pain relievers is similar to that of oxycodone products for the years 2002 through 2005. DEA expanded this analysis using additional OxyContin® product-specific NSDUH data (obtained from SAMHSA) to determine whether the lifetime users of oxycodone products, upon exclusion of the lifetime users of OxyContin®, a high strength extended-release product of oxycodone, differ from the lifetime users of hydrocodone combination products with regard to their propensity to use any pain relievers with in the past year. Another objective of this extended analysis is also to find out whether the lifetime users of OxyContin, had higher propensity as compared to the lifetime users of other drug categories to use any pain relievers for non-medical purpose with in the past year. These data are shown in Table 15. Percentages of lifetime users of specific pain relievers who used any pain reliever in the past year are shown in parentheses in Table 15 and also presented in Figure 15.

The data indicate that considerable numbers of lifetime users of pain relievers have used these drugs for non-medical purpose in the past year. For example, in 2006, about 12.64 million individuals among the lifetime users of any pain relievers used any pain relievers in the past year. Corresponding numbers for the lifetime users of oxycodone products and hydrocodone products categories were 5.78 million and 9.04 millions, respectively. About 2.58 million individuals among the lifetime users of OxyContin® used in the past year any pain reliever, while the corresponding number for the lifetime users of oxycodone products other than OxyContin® was 3.2 million in 2006.

Percentages of lifetime users of any pain relievers who used any pain relievers in the past year ranged from 35.4 to 37.8 during 2002 through 2006. Percentages of lifetime users of hydrocodone combination products (range: 42.7 % to 48.6%) and oxycodone products (range: 41.3% to 45%) who used any pain relievers in the past year are higher than those for lifetime users of any pain relievers during 2002 through 2006. Lifetime users of OxyContin® (range: 60.7% to 71%) had markedly higher incidence of any pain reliever use in the past year. Further analysis of data for the lifetime users of oxycodone products other than OxyContin® (schedule II) indicated that users of these products had incidences of past year use of any pain relievers (range: 33.4% to 36.6%) that are similar to those of the lifetime users of any pain relievers, but are considerably less than those of the lifetime users of hydrocodone combination products and all oxycodone products.

The above mentioned data suggest that the propensity of the lifetime users of OxyContin® to have used any pain relievers in the past year is markedly higher than that of the lifetime users of any pain relievers (about 1.7 to 1.9 fold), hydrocodone combination products (about 1.4 to 1.7 fold), oxycodone products (about 1.4 to 1.7 fold), and oxycodone products other than OxyContin® (about 1.7 to 2 fold). Lifetime users of oxycodone products other than OxyContin® (i.e., immediate-release single-entity products and immediate-release combination

products) are similar to the lifetime users of any pain relievers with regard to their incidence of past year use of any pain relievers, but are less (1.2 to 1.4 fold) than that of the lifetime users of hydrocodone products.

Table 15. Lifetime non-medical users of any pain relievers, hydrocodone combination products, OxyContin®, oxycodone products, and oxycodone products other than OxyContin® and the number of individuals among each of these categories who used any pain relievers for non-medical purpose in the past year[§]

Data Type	Drug Category	Numbers in Thousands (Percentages)*				
		2002	2003	2004	2005	2006
Lifetime Users of	*Any Pain Reliever*	29,611	31,207	31,768	32,692	33,472
	Hydrocodone Combination Products[1,2]	13,952	16,808	17,734	18,875	20,755
	OxyContin®	1,924	2,832	3,072	3,481	4,098
	Oxycodone Products[1,3]	10,151	11,538	11,925	12,029	12,858
	Oxycodone Products Other than OxyContin®	8,227	8,706	8,853	8,548	8,760
Any Past Year Pain Reliever Use Among Lifetime Users of	*Any Pain Reliever*	10,992 (37.1)	11,671 (37.4)	11,256 (35.4)	11,815 (36.1)	12,649 (37.8)
	Hydrocodone Combination Products[1,2]	6,782 (48.6)	7,679 (45.7)	7,768 (43.8)	8,068 (42.7)	9,039 (43.6)
	OxyContin®	1,366 (71.0)	1,837 (64.9)	2,042 (66.4)	2,112 (60.7)	2,581 (63.0)
	Oxycodone Products[1,3]	4,286 (42.2)	5,020 (43.5)	5,102 (42.8)	4,973 (41.3)	5,783 (45.0)
	Oxycodone Products Other than OxyContin®	2,920 (35.4)	3,183 (36.6)	3,060 (34.6)	2,861 (33.4)	3,202 (36.6)

*Values in parentheses indicate the number of persons in percentages who used any pain reliever in the past year among lifetime users of specific pain relievers.

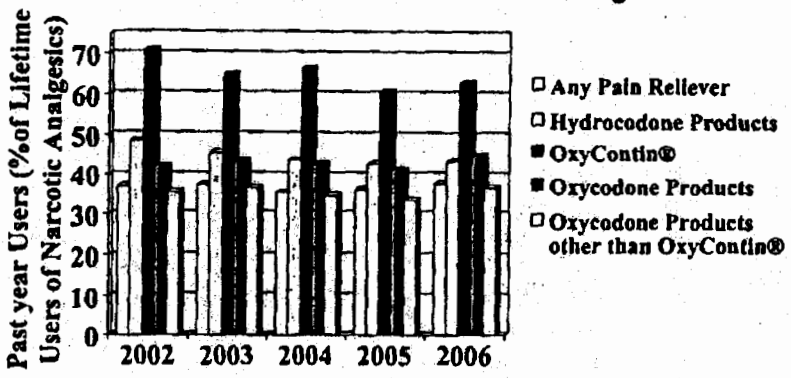
[1] Includes other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category.

[2] Includes Vicodin®, Lortab®, or Lorcet®, and hydrocodone.

[3] Includes Percocet®, Percodan® or Tylox®, and OxyContin®.

§In the U.S., nearly 100 percent (of total kilogram amounts distributed) of hydrocodone was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone was marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

Figure 15. Past Year Users of Any Pain Relievers Among Lifetime Users of Narcotic Analgesics[1]



Data Source: NSDUH

[1] Oxycodone products include Percocet®, Percodan® or Tylox®, and OxyContin® and other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category. Hydrocodone products include Vicodin®, Lortab®, or Lorcet®, and hydrocodone and other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category.

These data indicate that the lifetime users of hydrocodone combination products have higher propensity than that of lifetime users of oxycodone immediate-release products (schedule II) (single-entity and combination products combined) to have used for non-medical purpose any pain relievers in the past year. The lifetime users of OxyContin® had markedly high rates of past year use of any pain relievers as compared to that of the lifetime users of all other categories of pain relievers.

In summary, these NSDUH data collectively indicate that hydrocodone combination products have high abuse potential.

1.2.5.2. Monitoring the Future (MTF)

Monitoring the Future (MTF) is a questionnaire based survey of drug use among high school students conducted using a representative sample of students in the U.S. This survey does not provide individual opioid analgesic substance-specific information. Therefore, the rates of prevalence of abuse for hydrocodone and oxycodone among high school students could not be computed. However, MTF did provide product-specific information for two opioid analgesic products, namely Vicodin®, a hydrocodone combination product, and OxyContin®, an oxycodone extended-release product. Annual prevalence of the non-medical use of Vicodin® (ranges: 2.5 – 3.0% of 8th graders; 6.2 – 7.2% of 10th graders; 9.3% – 10.5% of 12th graders) was substantially higher than that of OxyContin® (ranges: 1.3 – 2.6% of 8th graders; 3.0 – 3.9% of 10th graders; 4.0% – 5.5% of 12th graders) for years 2002 through 2007. In 2007, the annual prevalences for Vicodin® among 8th, 10th and 12th graders were 2.7, 7.2 and 9.6 percent, respectively. The corresponding prevalences for OxyContin® were 1.8, 3.9 and 5.2 percent.

In summary, the aforementioned data from drug abuse surveys (NSDUH and MTF) collectively indicate high prevalence of abuse of hydrocodone combination products thereby indicating their high abuse potential.

1.2.6. Hydrocodone combination products are related in their action to other schedule II opioid analgesics drugs.

As described earlier in the document, recent clinical abuse liability studies have demonstrated that hydrocodone combination products (Hycodan® or hydrocodone in combination with acetaminophen) are similar to morphine (schedule II) with respect to abuse liability related pleasant as well as unpleasant effects (Zacny, 2003; Zacny et al., 2005). Current evidence also indicates that acetaminophen at clinically relevant doses lacks psychoactive effects. These data suggest that acetaminophen, a nonnarcotic analgesic ingredient present in over 90% of currently marketed hydrocodone combination products or homatropine, an anticholinergic drug present in another hydrocodone combination product (Hycodan®), do not appreciably alter the subjective effects of hydrocodone.

1.2.7. Other data sources

Numerous individual state health and law enforcement offices have contacted the DEA expressing concerns about the severity of the hydrocodone diversion and abuse problem within their state. The Community Epidemiology Work Group Report to the National Institute on Drug Abuse continues to mention about the diversion, abuse and deaths associated with hydrocodone.

Factor 1 Summary:

- Abuse liability of hydrocodone substance is similar to that of morphine. It is self-administered in animal models, will substitute for morphine in drug discrimination studies and produces effects that are substantially similar to morphine in both animals and humans.
- Physiological effects, subjective effects and drug "liking" scores produced by hydrocodone combination products (Hycodan® and hydrocodone and acetaminophen combination product) are substantially similar to those produced by morphine in humans.
- Acetaminophen, the nonnarcotic analgesic ingredient present in majority of hydrocodone combination products, at clinically relevant doses lacks psychoactive effects.
- There is no published scientific evidence suggesting that abuse potential of hydrocodone combination products is less than that of its substance, or of other standard schedule II opioid single-entity or combination products.
- Hydrocodone combination products are the most commonly prescribed pharmaceutical opioids in the U.S. with over 135 million prescriptions dispensed in 2007. Acetaminophen, a nonnarcotic analgesic, is present as a co-ingredient in over 90% of all hydrocodone combination products dispensed annually.
- Hydrocodone products have been in clinical use in the U.S. for over a half a century and were initially used primarily as cough suppressants. However, since 1990s, these are being increasingly used as analgesic drugs rather than as cough suppressants.
- A review of drug abuse indicators for hydrocodone combination products over the past several years indicates that these products are the most widely diverted and abused drugs in the country.

- Data from NSDUH indicate that individuals are abusing (past year initiates) hydrocodone combination products at rates (calculated per each kg of drug distributed) substantially higher than that of oxycodone products.
- According to the NSDUH, the combined data from 2002 through 2005 indicate that 57.7 percent of persons who first used pain relievers non-medically in the past year used hydrocodone combination products and 21.7 percent used oxycodone products.
- According to the NSDUH, percentages of the lifetime users of hydrocodone combination products reporting past year use of any pain reliever for non-medical purpose are higher than those of the lifetime users of oxycodone products other than OxyContin® (i.e., oxycodone immediate-release products) from 2002 through 2006.
- Data from NFLIS and STRIDE indicate that the rates of diversion (calculated as cases or exhibits per kilogram amounts of drug distributed) of hydrocodone combination products are similar to or slightly larger than those of oxycodone products.
- Data from DAWN indicate that the rates of abuse related adverse health consequences (calculated as ED mentions per kilogram amounts of drug distributed) for hydrocodone combination products are similar (during 1998 through 2002) to or slightly higher (during 2004 through 2006) than those for oxycodone products.
- Medical Examiner data from FDLE indicate that hydrocodone combination products, similar to oxycodone products, have been associated with large number of deaths in Florida. The rates of deaths (calculated per each 100 kg of drug distributed in Florida) associated with hydrocodone combination products are similar to those for oxycodone products.
- Data from NPDS indicate that annual toxic exposures involving hydrocodone combination products consistently exceeded those for oxycodone products. According to NPDS, rates of toxic exposures (calculated per each 100 kg of drug distributed) involving hydrocodone combination products are higher than those involving oxycodone products.
- Data from MTF indicate that a substantial percentage of young Americans (high school students) use hydrocodone combination products for non medical purposes. Annual prevalence of the non-medical use of Vicodin® (range: 9.3% – 10.5% of 12th graders for years 2002 through 2007), a hydrocodone combination product, was substantially higher than that of OxyContin® (range: 4.0% – 5.5% of 12th graders for years 2002 through 2007), an oxycodone extended-release product, in recent years.
- The current widespread abuse of hydrocodone combination products and clinical studies reporting similar subjective and other psychoactive effects for both hydrocodone combination products and morphine and the DEA analyses of rates of drug abuse relative to amounts (kg) of drug distributed (as reported in ARCOS database) collectively suggest that the non-narcotic drugs present in hydrocodone combinations products do not reduce the abuse potential of hydrocodone.

Conclusion

The above information collectively demonstrates that hydrocodone combination products have high potential for abuse similar to oxycodone products controlled in schedule II of the CSA.

2. Scientific Evidence of Its Pharmacological Effects, If Known

DHHS review document provided scientific evidence of pharmacological effects of hydrocodone and of a number of other nonnarcotic active ingredients that are present in the currently marketed hydrocodone combination products. DHHS findings indicate that hydrocodone is marketed primarily in fixed combinations with nonopioid drugs, namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine methylbromide.

Combination products of hydrocodone with non steroidal anti-inflammatory drugs (NSAIDs) are indicated for the management of moderate to moderately severe pain, while the combination products of hydrocodone with homatropine or chlorpheniramine are used for the relief of cough. Mechanism of action of hydrocodone as an analgesic and cough suppressant is different from those of other nonnarcotic active ingredients present in these formulations. NSAIDs in large part produce analgesic, antipyretic and anti-inflammatory effects through inhibition of cyclooxygenase-2 (COX-2) enzyme.

Hydrocodone, similar to other morphine-like drugs, selectively binds to μ opioid receptors. Hydrocodone has a higher affinity than oxycodone and codeine and acts as a full agonist at these receptors (Chen *et al.*, 1991; Kotzer *et al.*, 2000; Thompson *et al.*, 2004). Activation of μ opioid receptors mediates the analgesic and antitussive effects of hydrocodone. Analgesic effect of 30 mg of orally administered hydrocodone bitartrate is approximately equal to that of 30 mg of oxycodone hydrochloride (Gutstein and Akil, 2006). Similarly, hydrocodone bitartrate has been shown to be equipotent or slightly less potent than oxycodone hydrochloride in producing abuse liability related subjective effects (Walsh et al., 2008).

According to the DHHS review document, different mechanisms of pharmacological actions of hydrocodone versus NSAIDs underlie the enhanced analgesic effects of their combination products compared to the analgesic effects of individual ingredients. The rationale for combining hydrocodone with NSAIDs include (i) additive or synergistic effects as a result of different mechanisms of actions of individual ingredients present in these combination products; (ii) use of reduced doses of individual ingredients and thus reduced adverse reactions, and (iii) increased patient compliance (Beaver, 1984). Hydrocodone and acetaminophen combination provide better pain relief compared to either hydrocodone or acetaminophen alone (Beaver and McMillan, 1980). While acetaminophen is well tolerated with a low incidence of gastrointestinal side effects, acute overdose can cause severe hepatic damage, coma and death.

Hydrocodone bitartrate (dihydrocodeinone) was synthesized in the early 1920s and was shown to be an effective antitussive and analgesic agent at doses as low as 10 to 15 mg (Hopkinson, 1978a, b). Early studies demonstrated that the subcutaneous administration of hydrocodone was more effective than codeine as an antitussive agent. Throughout the 1920s numerous studies, mostly conducted in Germany, concluded that hydrocodone was a potent and effective compound for the treatment of cough and pain (see review by Krueger *et al.*, 1943). Krueger *et al.* (1943) translated and reviewed these early German reports relating to hydrocodone's analgesic effects - analgesia had been demonstrated with orally- and subcutaneously- administered doses as low as 5 mg; successful pain control had been achieved

with a dose range of 5 to 20 mg. Reynolds and Randall (1959) claimed that a dose of 15 mg of hydrocodone is equivalent to 10 mg of morphine for pain relief in humans.

In summary, hydrocodone's pharmacological effects are similar to other μ opioid receptor agonists. It is effective as an antitussive agent and as an analgesic for the treatment of moderate to moderately severe pain.

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance

DHHS reviewed chemical and toxicological properties of hydrocodone and nonnarcotic components of hydrocodone combination products. Chemically, hydrocodone, also known as dihydrocodeinone, is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one, CAS [125-29-1], $C_{18}H_{21}NO_3$; molecular weight 299.36. It is a semisynthetic opioid derived from naturally occurring opioid alkaloid codeine. The bitartrate salt of hydrocodone, CAS [34195-34-1], is the main active co-ingredient in all the hydrocodone combination products currently marketed as analgesics. Hydrocodone bitartrate occurs as fine, white crystals or crystalline powder and is soluble in water and slightly soluble in alcohol. The sulfonated styrene-divinylbenzene copolymer complex with hydrocodone, also known as hydrocodone polistirex, is the derivative used in combination with chlorpheniramine polistirex as an antitussive. Some common adverse effects of hydrocodone substances are lightheadedness, dizziness, sedation, nausea and vomiting, constipation, rash, pruritus, euphoria, and dysphoria. Abuse of hydrocodone may lead to tolerance to some or all of the adverse effects, in addition to dependence.

Acetaminophen is N-(4-hydroxyphenyl) acetamide, CAS [103-90-2]; molecular weight 151.16. Slightly soluble in cold water, more soluble in hot water, soluble in methanol, ethanol, dimethylformamide, ethylene dichloride, acetone, ethyl acetate, slightly soluble in ether and insoluble in petroleum ether, pentane and benzene. Most serious adverse effect of acute overdosage of acetaminophen is dose-dependent, potentially fatal hepatic necrosis. In adults, hepatotoxicity may occur after ingestion of a single dose of 10 to 15 g (140 to 250 mg/kg) of acetaminophen; doses of 20 to 25 g are potentially fatal. Symptoms during the first 2 days of acute poisoning by acetaminophen do not reflect the potential seriousness of the intoxication. Nausea, vomiting, anorexia and abdominal pain occur in the first 24 hours and persist for a week. Clinical indications of hepatic damage manifest themselves within 2-4 days after ingestion of a toxic dose.

Chlorpheniramine is an antihistamine used in hydrocodone antitussive formulations to relieve itchy watery eyes and runny nose associated with colds. According to DHHS, the most common adverse effect of chlorpheniramine is central nervous system depression evidenced by drowsiness, lethargy, fatigue, hypnosis, and coma. Related effects include vertigo, ataxia, tinnitus (ringing in ears), and blurred vision.

Homatropine methylbromide is an atropine-like anticholinergic medication that inhibits muscarinic acetylcholine receptors. It is less potent than atropine and has a shorter duration of action. According to DHHS review document, the most common adverse effects of homatropine include dry mouth, dilation of pupils, bradycardia followed by tachycardia, cardiac palpitations

and arrhythmias and constipation and these are dose-related. In overdose, peripheral effects become more pronounced causing hyperthermia, hypertension, increased respiration, nausea and vomiting. Homatropine is placed in subtherapeutic amounts in hydrocodone cough preparations to inhibit high dose use of these medications.

Summary:

Hydrocodone is a semisynthetic opioid. The bitartrate salt form of hydrocodone is the main active component in all currently marketed hydrocodone combination products. The primary nonnarcotic analgesic combined with hydrocodone is acetaminophen and accounts for about 90% of all hydrocodone combination products currently marketed. Other nonnarcotic drugs present as co-ingredients are aspirin, ibuprofen, chlorpheniramine or homatropine. These nonnarcotic drugs at high doses produce adverse effects. However, there is no published scientific evidence to support the assumption that these drugs could significantly reduce the abuse liability effects of hydrocodone. Further, the increasing incidents of actual abuse data, as documented in Factor 1, demonstrate that hydrocodone combination products, despite the potential adverse effects of their nonnarcotic ingredients, have high potential for abuse.

4. Its History and Current Pattern of Abuse

4.1. History and pattern of abuse prior to the enactment of the CSA

There were numerous published reports of abuse of hydrocodone in Germany in 1920s and 30s (Eddy *et al.,* 1957). In 1943, a comprehensive review of the German literature by Krueger and his associates revealed a series of reports of hydrocodone addiction. In their report to the League of Nations in 1939, the Advisory Committee on Traffic in Opium and Other Dangerous Drugs reported that hydrocodone produced euphoria "but there is no doubt, as has been said before, that cases of addiction to Dicodid (hydrocodone) are known (p. 412)."

Data regarding the pharmacological effects of hydrocodone substance and its high potential for abuse were available prior to the enactment of the CSA and the placement of hydrocodone in schedule II reflects that knowledge base. At the time the CSA was passed, hydrocodone combination products were primarily utilized as cough suppressants and were not widely prescribed. As mentioned earlier, U.S. Congress presumably viewed that the addition of nonnarcotic ingredients (within the specified dose limits as specified in the CSA) in hydrocodone combination products reduced abuse potential of hydrocodone. This is evident from the fact that hydrocodone combination products were controlled in schedule III.

4.2. History and pattern of abuse following the enactment of the CSA

It was not until the 1990s that hydrocodone started to be widely used as an analgesic and also widely abused for its opioid effects. According to the DEA's ARCOS data (see Factor 1), a total of about 32,971 kg of hydrocodone (54,050 kg of hydrocodone bitartrate salt equivalent) were sold to end-user registrants (pharmacies, doctors, hospitals, teaching institutions, and narcotic treatment centers) in 2007. The annual consumption of hydrocodone (as bitartrate salt) exceeded that of oxycodone (47,753 kg as oxycodone hydrochloride salt) by about 13% in 2007.

These amounts of hydrocodone and oxycodone are the total amounts available for both medical and non-medical use, as these drug substances are not clandestinely produced nor does DEA have any evidence of that either drug is illicitly imported into the U.S. in any significant amount.

Since the 1990s, hydrocodone has been increasingly used as analgesic as evident from increase in total prescriptions for hydrocodone analgesic combination products (NPA*Plus*™; formerly known as IMS Health Inc.). During this period, there was also corresponding increase in misuse and abuse of hydrocodone combination products as indicated by data from national surveys, poison control centers, forensic laboratory and DAWN data (see factor 1). Hydrocodone is abused by individuals of diverse ages from adolescents to older populations. The MTF surveys indicate that nearly 10% of high school seniors used hydrocodone for non-medical purposes in 2007.

4.3. Actual abuse reported in published medical literature

One of the first reports of abuse of hydrocodone in the United States was published in 1961 and described 45 cases of abuse in a district populated with less than 25,000 inhabitants (Rosenwald and Russel, 1961). In this early report, the physicians claimed that most of the criteria for opioid addiction were fulfilled by each of the 45 abusers, each complained of dependence and withdrawal symptoms once the drug was removed and that relapse was common. These authors claimed that hydrocodone was an increasing substitute for the "higher narcotics."

Cicero *et al.* (2005) collected prescription opioid abuse data for a number of drugs on quarterly basis from drug abuse experts (representatives of the nation's methadone programs, treatment centers, impaired health care professional programs, NIDA grantees and high-prescribing physicians) as responses to questionnaire about drug abuse patterns of individuals in about 21% of the nation's 973 three digit zip codes. These authors found that abuse of OxyContin® and hydrocodone combination products is by far the most prevalent followed by other oxycodone products (oxycodone immediate-release and combination products), methadone, morphine, hydromorphone, fentanyl and buprenorphine. Cicero and his associates (Cicero *et al.*, 2007a and 2007b) further studied the relationship between prescribed use of a number of opioid analgesics and their non-medical use (abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, DSM IV criteria) data as gathered from drug treatment centers located in 165 of the nation's 997 three digit postal ZIP codes representing urban, suburban, and rural locations distributed across the country. These authors found a strong correlation between therapeutic exposure to opioid analgesics and their abuse. These authors found that hydrocodone was the most prescribed (number of patients) opioid analgesic followed by immediate-release oxycodone, extended-release oxycodone, morphine/methadone, fentanyl, hydromorphone and buprenorphine in the descending order. Rates of abuse, expressed as cases per 100,000 populations, were the highest for hydrocodone products and extended-release oxycodone products, while the rest of opioid analgesics, including immediate-release oxycodone products had much lower rates.

Cicero and his associates (Cicero *et al.*, 2007a and 2007b) further found that extended-release oxycodone, buprenorphine, hydromorphone and methadone had high rates compared to

hydrocodone combination products and immediate-release oxycodone products (schedule II), when rates were calculated as cases per 1000 patients who received a given opioid analgesic. Hydrocodone combination products and immediate-release oxycodone products had similar (time-course graphs overlapped each other), but low rates of abuse in this analysis that utilized number of patients as denominator. These authors suggested that rates of abuse calculated as cases per 1000 patients who received a given opioid provide a measure of drug risk (abuse)-benefit (appropriate analgesia) profile. However, it is important to note that populations represented in the numerator (abusers who may include patients as well as other individuals who have not received a legitimate prescription) are not identical to those represented in the denominator (patients only). Further, patient populations are also not homogenous. For example, patients receiving methadone and buprenorphine are typically opioid addicts and thus already have preexisting risk of opioid addiction and are likely to have history of drug diversion. Patients receiving high strength OxyContin® are likely to be opioid tolerant and suffering from chronic severe pain, while those receiving hydrocodone combination products and immediate-release oxycodone products are typically opioid-naïve (non-tolerant) suffering from acute or chronic pain of moderate intensity. For these reasons, DEA provided additional data analyses to normalize rates using total kilograms as denominator.

Hughes *et al.* (2007) collected and analyzed data about intentional exposure (abuse, intentional misuse, suicide, or intentional unknown) calls to eight geographically dispersed poison centers (serving about 65 million U.S. population) for a period of twelve months (December 29, 2002 through December 27, 2003) for a number of opioid analgesics. These authors found that rates of abuse was highest for hydrocodone at 3.75 per 100,000 population followed by oxycodone at 1.81 per 100,000. Hydrocodone was involved in 55% of all of the intentional exposure cases, where as oxycodone was involved in 27%. Following exclusion of suicide cases from the data analysis, hydrocodone was still the most commonly abused opioid. These authors discussed that higher rates of hydrocodone abuse might be attributed to less restrained regulation due to their schedule III control status (prescriptions may be phoned in). These authors also suggested that population-based rates of abuse illustrate the absolute burden posed by the drug misuse and abuse on the population as a whole. This analysis is appropriate for addressing public health burden and was utilized in Factor 6 of this review. However, it does not address the drug availability.

4.4. Street prices – Diversion Quarterly Reports of DEA

Quarterly Reports submitted in 2007 by all DEA Diversion Group Supervisors indicate that hydrocodone combination products are commonly diverted in every geographic area of the country and are the most sought after licit drugs throughout all domestic field offices of DEA. Recent street prices ranged from as low as $0.1 per tablet in Fort Myers/Naples, Florida to as high as $40 per tablet in Knoxville, South Carolina. Brand name products most frequently encountered on the street include Vicodin®, Lorcet®, and Lortab®. DEA case reports document the diversion of hydrocodone combination products by pharmacy theft, doctor shopping, bogus call-in prescriptions, fraudulent or altered prescriptions, and by registrants (see appendix for brief summaries of a sampling of case files).

Summary

Soon after introduction for clinical use, there were reports of hydrocodone abuse and addiction. By 1950s, it was well established that hydrocodone had an abuse liability similar to that of morphine. In U.S., popularity of hydrocodone as a drug of abuse increased in the 1990s coinciding with its increasing use as analgesic. Currently hydrocodone combination products are widely diverted and abused throughout the U.S as demonstrated in national and regional drug abuse databases (see Factor 1 and Appendix 1). The additional fact that hydrocodone combination products are the most encountered opioid analgesic by law enforcement and have a street value demonstrate their high abuse potential.

5. THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE

Since the initial reports published in 1960s about abuse of hydrocodone in the United States (Rosenwald and Russel, 1961; Statement of the Committee on Drug Addiction and Narcotics, 1963), its abuse has continued although widespread diversion, trafficking, and abuse of hydrocodone products were not evident until the 1990s. By late 1990s, there were large increases in the diversion and abuse of hydrocodone products.

Today, hydrocodone-combination products are associated with significant illicit activity and abuse. Federal, state and local forensic laboratory data rank hydrocodone as the most frequently encountered opioid pharmaceutical in submissions to the laboratories (see Factor 1). For example, in 2007, there were over 29,000 exhibits for hydrocodone (NFLIS). All divisions of the DEA across the U.S. have reported that hydrocodone combination products are among the most sought after pharmaceuticals. In 2006, according to the poison control centers data (NPDS), there were over 22,000 toxic exposures involving hydrocodone. In 2002, there were over 25,000 DAWN ED mentions associated with hydrocodone and it was ranked sixth among all controlled substances. A number of data sources (See Factor 1) indicate that hydrocodone associated deaths are significant and increasing. According to the NSDUH, a national survey on drug misuse and abuse among individuals age 12 and older, there were large number of lifetime and past year initiates of hydrocodone for non-medical purpose and these numbers exceeded those of oxycodone. According to the MTF, nearly 10% of high school seniors reported non-medical use of Vicodin®, a hydrocodone combination product.

The Appendix 1 lists annotated case histories of a sampling of hydrocodone diversion cases characterized by DEA communications from its field offices from 1994 through March 2008. These summaries reflect only those cases that were entirely federal or in which federal assistance was involved. The majority of cases involve diversion by health care professionals (nurses, doctors, pharmacists, etc.). In addition, these cases document a number of illegal activities including drug theft, doctor shopping, "bogus call-in" prescriptions by individuals illicitly using DEA registration numbers, diversion by registrants, fraudulent prescriptions and various drug trafficking schemes. While these methods of diversion are not unique, the number of cases involving hydrocodone and the amounts of hydrocodone diverted from legitimate channels are significant.

6.1. Pharmaceutical investigations data - DEA

In 2003, The Geo-Drug Enforcement Program (G-DEP) codes were assigned by DEA in May 2003 for hydrocodone and oxycodone to track and maintain statistical information about their diversion and trafficking cases and related information. Thus the full year data has become available since the first quarter of 2004 and is presented in the Table 16 below.

Table 16. Pharmaceutical investigations involving hydrocodone and oxycodone.§

Year	Hydrocodone			Oxycodone		
	Cases	Arrests	Convictions	Cases	Arrests	Convictions
2004	220	111	24	181	140	27
2005	265	201	97	198	254	97
2006	341	256	129	219	245	147
2007	301	210	137	256	356	148
Totals (2004-2007)	**1,127**	**778**	**387**	**854**	**995**	**419**

§ The data are obtained from The Statistical Management Analysis and Reporting Tools System (SMARTS), a DEA database that provides a single interface for retrieving and analyzing information on its enforcement activities. (i.e., case initiation, suspect arrest, suspect disposition, asset seizure, drug removal, associated DEA agent work hours).

Annual total cases involving diversion of hydrocodone combination products consistently exceeded those for oxycodone for years 2004 through 2007. Total cases involving hydrocodone combination products (1,127) for years 2004 through 2007 were over 30% more than those involving oxycodone products (854) for the same time period. Cases involving hydrocodone combination products resulted in 778 arrests leading to 387 convictions, while cases involving oxycodone products resulted in 995 arrests leading to 419 convictions.

Summary

In 1963, a report to the Committee on Drug Dependence provided evidence of outbreaks of hydrocodone abuse. Since 1990s, the diversion and abuse of hydrocodone has escalated in the country. It is currently the most diverted and abused pharmaceutical opioid analgesic. Total number of DEA cases involving hydrocodone exceeded those for oxycodone from 2004 through 2007. DEA case investigations documented numerous methods of diversion of hydrocodone. These methods involved drug theft, doctor shopping, "bogus call-in" prescriptions, fraudulent prescriptions, diversion by registrants, and various drug trafficking schemes.

6. WHAT, IF ANY, RISKS ARE THERE TO PUBLIC HEALTH

Despite the medical value of hydrocodone combination products as antitussive and analgesic drugs, the misuse and abuse of these products present a number of risks to the public health. Many of the risk factors associated with these products are common risks shared with other μ opioid receptor agonists. These include the risks of developing tolerance, dependence

and addiction and the attendant problems associated with these risks. Another important risk factor associated with hydrocodone combination products is limited to nonnarcotic active ingredients and their potential to cause toxicity in high doses. According to the DHHS review document, all the nonnarcotic active ingredients that are present in currently marketed hydrocodone combination products have potential to cause adverse health consequences when ingested large doses. Among these nonnarcotic active ingredients, acetaminophen related toxicity is of particular importance. This is due to the fact that about 90% of all hydrocodone combination products contain acetaminophen as nonnarcotic active ingredient.

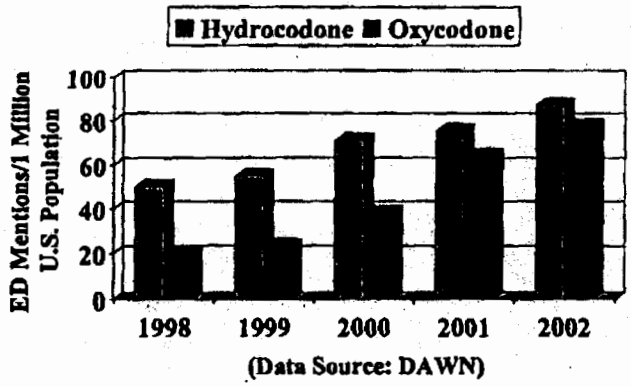
Hydrocodone's pharmacological effects, including analgesia, cough suppression, and subjective effects (i.e., euphoria and drug liking), are most likely attributable to its own intrinsic efficacy at μ opioid receptors. In a majority of the standard behavioral assays, hydrocodone has been found to be more similar to morphine, hydromorphone, and oxycodone than to codeine with an abuse potential equivalent to morphine.

Investigators from Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS), a research program to develop methods to detect the abuse and diversion of opioid analgesics, published a series of reports suggesting that rates of abuse, calculated as the ratio of abuse cases involving a given drug relative to the total population, provide a measure of public health burden resulting from its abuse and misuse on the population as a whole (Hughes *et al.*, 2007; Cicero *et al.*, 2005, 2007a, 2007b; Passik and Kirsh, 2007; Smith *et al.*, 2007). In the present evaluation, DEA utilized this ratio to estimate the public health burden (as defined by these investigators) posed by hydrocodone combination products and results of these analyses are presented below.

6.1. Drug Abuse Warning Network (DAWN) emergency department data

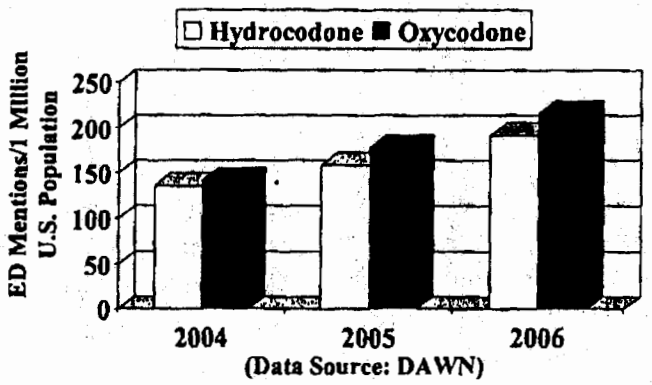
According to the DAWN, ED mentions associated with hydrocodone and oxycodone are the highest among all opioid analgesics, with hydrocodone mentions being the larger of the two (see Factor 1). The rates of ED mentions, calculated as the number of annual ED mentions per 100,000 populations, for hydrocodone and oxycodone are shown in Figure 16 (data from 1998 through 2002) and Figure 17 (data for 2004, 2005 and 2006). These analyses suggest that the rates of ED mentions associated with hydrocodone are largely (1998 through 2000) slightly higher (2001 and 2002) or slightly lower (2005 and 2006) than those for oxycodone.

Figure 16. Emergency Department Mentions/1 Million U.S. Population



(Data Source: DAWN)

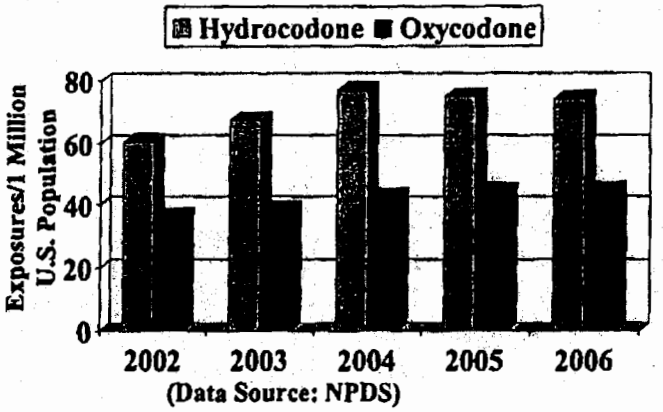
Figure 17. Emergency Department Mentions/1 Million U.S. Population



6.2. Poison control centers data

According to the annual reports of NPDS for the past several years, the number of hydrocodone toxic exposures and associated deaths were the largest followed by oxycodone among opioid analgesic drugs (see Factor 1). For example, the rates of toxic exposures, calculated as exposures per 100,000 populations, for hydrocodone exceeded those for oxycodone in recent years (Figure 18).

Figure 18. Drug Toxic Exposures/1 Million U.S. Population



The data from DAWN and NPDS collectively suggest that the public health burden associated with hydrocodone combination products exceeded that of oxycodone products.

6.3. Adverse Event Reporting System (AERS) data

DHHS review document provided adverse events data from AERS database for selected opioids including hydrocodone and oxycodone in a drug-specific manner, though it stated that caution should be exercised when comparing drug safety issues because of a number of major limitations of this database. In addition to these limitations cited by the DHHS, the use of AERS data as presented in the DHHS review document further compounded the evaluation due to the following variables and reasons.

One important variable is FDA's approval of new products for marketing. Numbers of AERS reports for drugs with New Drug Applications (NDAs) are likely to be higher than those for drugs that had no new NDA's. This is particularly relevant again for the present review. For example, since the enactment of CSA in 1971, there are no new NDA's for hydrocodone, while there were NDAs for oxycodone (e.g. approval of oxycodone high strength extended-release product namely, OxyContin® in mid 1990s).

Second variable is the presence of drug products approved with mandatory risk management programs. Such products are likely to be reported at rates higher than those for products with no risk management program. In this context, it is important to note that OxyContin®, unlike hydrocodone products, is marketed with risk management program. Another variable, as mentioned in the DHHS review, is the nature and the degree of coverage in public media about adverse health effects of a particular product can increase the product-specific awareness and thus can affect reporting. This is particularly relevant to the present review because OxyContin®, an oxycodone extended-release product, received since late 1990s wide publicity in the media about its high potential to cause addiction and other adverse health effects and its high popularity among drug abuser population.

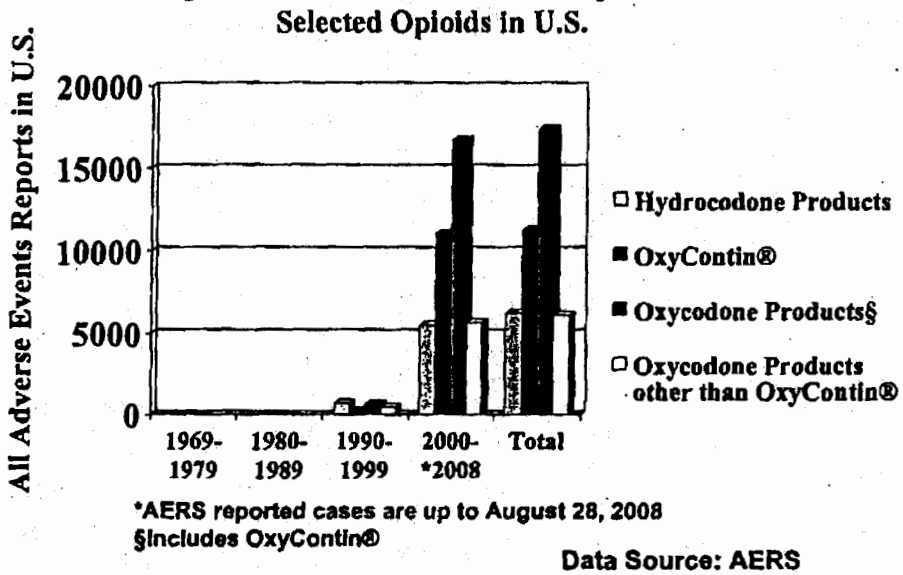
Of particular importance is another variable namely the amount of drug present in a given dosage unit of a given product. Oxycodone single-entity extended-release formulation, OxyContin®, contains large amounts up to 80 mg oxycodone per each dose unit. Because dependence producing properties of a given opioid analgesic is a function of its dose, such product is likely to possess higher potential to cause abuse/dependence disorder than its moderate strength immediate-release single-entity products or its low strength combination products. In fact, as mentioned earlier, DEA's analysis of drug dependence data obtained from NSDUH revealed that the incidence of substance use disorder (i.e., dependence on or abuse of a substance) is markedly higher among lifetime users of OxyContin® as compared to the corresponding data among lifetime users of other oxycodone products (excluding OxyContin® lifetime users) or hydrocodone combination products.

For the above mentioned reasons, DEA calculated the AERS data for oxycodone products other than OxyContin® by subtracting the AERS data for OxyContin® from that of all oxycodone products. Also presented were the data for hydrocodone combination products. (Table 17). All adverse event data for these products was also presented temporally as 10-year blocks in Figure 19. According to this analysis, although adverse event reports received from 1969 though August 28, 2008 for all oxycodone products exceeded those for hydrocodone combination products, OxyContin® was mentioned in nearly two thirds of adverse event reports associated with all oxycodone products. Upon exclusion of OxyContin® associated reports, all adverse event reports for the remaining oxycodone products (oxycodone immediate release single-entity and combination products) were similar to those for hydrocodone combination products. Further majority of adverse events reported during this period (1969 -2008) for hydrocodone combination products (88%), OxyContin®(98%), all oxycodone products (96%) oxycodone products other than OxyContin® (92%) occurred mainly within the last 10 years.

Table 17. AERS data for hydrocodone combination products, OxyContin®, oxycodone products, and oxycodone products other than OxyContin® reported since 1969 to August 28, 2008.

Drug	All Adverse Event Reports	Overdose Reports (% of All Adverse Event Reports)	Completed Suicide Reports (% of All Adverse Event Reports)	Abuse and Dependence Reports (% of All Adverse Event Reports)
Hydrocodone Combination Products	6,232	1,871 (30%)	1,152 (18.5%)	829 (13.3%)
OxyContin®	11,282	2,413 (21.4%)	149 (1.3%)	6,191 (54.9%)
All Oxycodone Products including OxyContin®	17,400	5,073 (29.2%)	873 (5%)	7,026 (40.4%)
Oxycodone Products other than OxyContin®	6,118	2,660 (43.5%)	724 (11.8%)	835 (13.6%)

Figure 19. All Adverse Events Reports for Selected Opioids in U.S.



Of particular importance is the finding that the primary risk factor for hydrocodone combination products, similar to oxycodone products other than OxyContin®, was overdose. In contrast majority of OxyContin® associated adverse event reports (54.9%) involved abuse and dependence events (Table 17). Further, the abuse and dependence reports associated with

hydrocodone combination products expressed as a percentage of its corresponding all adverse events (13.3%) were similar to those for oxycodone products other than OxyContin® (13.6%).

Figure 20. All Adverse Events Reports for Selected Opioids in U.S. (1998-2008*)

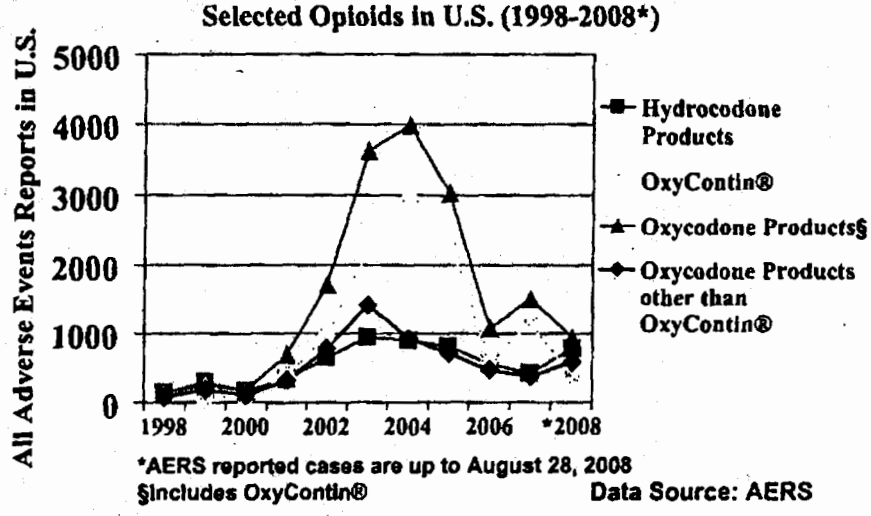
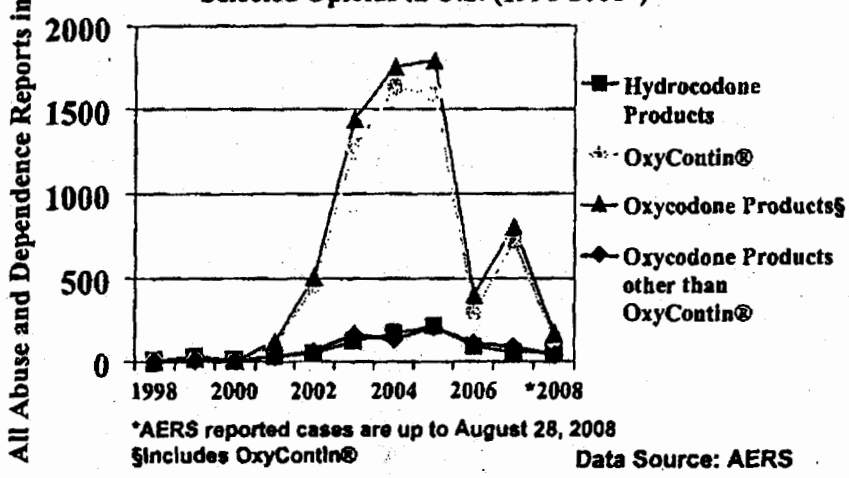


Figure 21. All Abuse and Dependence Reports for Selected Opioids in U.S. (1998-2008*)



Majority of adverse events for both hydrocodone combination products (88%) and oxycodone products (96%) were reported within the last 10 years (Figure 19). Thus, the temporal distribution of annual data of all adverse events and abuse and dependence events reported since 1998 for these products were also presented in Figures 20 and 21. These data show that all adverse events and abuse and dependence events associated with OxyContin® markedly increased beginning in 2001 with the peak increases occurring in 2004. In contrast, the corresponding increases for hydrocodone combination products and oxycodone products other than OxyContin® were significantly smaller in magnitude as compared to those for OxyContin®. Further, the time-course curves for hydrocodone combination products nearly overlapped with those for oxycodone products other than OxyContin®.

In summary, the adverse event report profile for hydrocodone combination products are similar to those for oxycodone products other than OxyContin® (oxycodone immediate release single-entity and combination products), but different from that of OxyContin®. Further, the fact that adverse reactions are still being reported for "old" (hydrocodone) drug products demonstrates its risks for adverse health effects. Hydrocodone combination products, due to their high abuse potential, are associated with significant public health risks.

DHHS review document mentioned a number of adverse health risks including hepatic necrosis and death associated with acetaminophen toxicity. In addition, recent studies indicate that hydrocodone and acetaminophen combination product cause hearing loss and this toxicity has been linked to acetaminophen content of this combination product (Friedman *et al.*, 2000; Oh *et al.*, 2000).

Summary

Public health risks associated with hydrocodone combination products are similar to those for oxycodone products other than OxyContin®,

7. Its Psychic or Physiological Dependence Liability

7.1. Animal studies

7.1.1. Psychic or physiological dependence of hydrocodone substance

Deneau & Seevers (1955), reported that hydrocodone (Dicodid, dihydrocodeinone), is similar to hydromorphone (Dilaudid®) in suppressing the abstinence signs elicited by chronic administration followed by abrupt withdrawal of morphine (3 mg/kg every 6 hours for 8 to 12 months) in monkeys. These authors further showed that abrupt drug withdrawal following prolonged daily administration of hydrocodone (0.75 mg/kg, every four hours for 30 days), similar to other opioid analgesic drugs including morphine and hydromorphone, elicits abstinence signs in monkeys. Nalorphine, an opioid antagonist, induced abstinence signs in these monkeys. These authors concluded that these results were similar to those results obtained in man (Seevers and Deneau, 1956). Deneau, McCarthy & Seevers (1959) further reported that hydrocodone is more potent than morphine in suppressing morphine abstinence in monkeys and equipotent to morphine in man.

Self-administration of drugs by animals is a valid predictor of abuse liability of dependence producing drugs. Using this animal model, it has been shown that rats initiate and maintain lever-press responding for intravenous self-administration of hydrocodone at a dose of 0.16 mg/kg/injection. The dose-dependent changes in the number of self-infusions administered in hourly test sessions were similar to those seen when morphine was self-administered in the rat. These data would predict a high psychic dependence liability for hydrocodone in humans (Tomkins et al., 1997).

7.1.2. Psychic or physiological dependence of hydrocodone combination products

The above mentioned animal studies predict that hydrocodone substance, similar to other schedule II opioid analgesics, has potential to cause severe psychic or physiological dependence and are consistent with the placement of hydrocodone substance in schedule II. Because animal studies are typically conducted for substances, but not for their pharmaceutical formulations, there are no published studies addressing the psychic or physiological dependence liability of hydrocodone combination products in animals. However, recent clinical studies as discussed later in this section indicate that nonnarcotic active ingredients in hydrocodone combination products do not alter the reward related subjective effects of hydrocodone. Therefore, hydrocodone combination products upon chronic use have potential to produce severe psychic or physiological dependence similar to that produced by hydrocodone substance.

7.2. Human studies

7.2.1. Psychic or physiological dependence of hydrocodone substance

In 1943, Krueger *et al.* reviewed scientific reports published in 1920s and 1930s by German scientists and found a series of reports of hydrocodone addiction. During the period from November 1949 through March 1950, the Committee on Drug Addiction and Narcotics of the National Research Council was called upon for evaluation and recommendations concerning the efficacy and dependence producing potential of hydrocodone and other narcotics. This committee found that hydrocodone was morphine-like in its dependence liability.

Isbell (1949) in his report to the 5th meeting of the Committee on Drug Addiction and Narcotics (one of the 15 medical advisory committees of the National Research Council) stated that subjective effects (including euphoria) of hydrocodone (30 to 40 mg) are similar to that of morphine, Dilaudid® and methadone when tested in 6 former opioid addicts. With regard to hydrocodone addiction liability, committee concluded that:

> Because it produces unmistakable intense euphoria, because it will relieve the syndrome of abstinence from morphine, and because mild to severe symptoms of abstinence follow abrupt withdrawal of dihydrocodeinone after experimental addiction of 38 days duration, dihydrocodeinone must be regarded as possessing addiction liability which more nearly approaches the addiction liability of morphine than it does the addiction liability of codeine

In early human studies conducted in the U.S., it was found that hydrocodone (45 mg) produces a sharp decline in the intensity of the opioid withdrawal syndrome for 6 to 8 hours after its administration in two morphine (chronically administered 480 mg per day) dependent subjects undergoing spontaneous withdrawal. It was also found that in five male subjects with history morphine addiction maintained on 240 mg (60 mg q.i.d., SC) hydrocodone produces physiological (miosis and EEG changes) and subjective (drug liking) effects similar to those of morphine in five male subjects with history of morphine addiction. Upon abrupt withdrawal of hydrocodone, these subjects experienced withdrawal syndrome similar, but milder, than that of morphine, but more pronounced than that of codeine. Based on these data, these authors

concluded that the addictive liability of hydrocodone is more similar to morphine than to codeine (Isbell, 1949; Fraser and Isbell, 1950).

Jasinski and Martin (1967) tested hydrocodone for its ability to suppress the signs and symptoms of opioid abstinence syndrome in seven subjects chronically administered 240 mg of morphine sulfate per day. Abstinence was assessed from the 14th through the 24th hr after the last dose of morphine was administered using an 11-point scale. Hydrocodone was able to substitute for morphine and diminish the intensity of the abstinence syndrome.

The above mentioned data indicate that hydrocodone, similar to morphine, has potential to cause severe physiological dependence in humans and is consistent with the control of hydrocodone substance as schedule II of the CSA.

7.2.2. Psychic or physiological dependence of hydrocodone combination products

7.2.2.1. National Survey on Drug Use and Health

The DHHS review document provided NSDUH data from 2002 through 2005 with regard to the number of individuals that met criteria for substance use disorder (abuse or addiction) on any pain relievers among lifetime users of different narcotic analgesics products. DEA obtained from the Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA) additional data from 2002 through 2006 (Table 18).

NSDUH uses the criteria specified in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) (American Psychiatric Association, 1994) to classify individuals as dependent on or abusing specific substances. Percentages of lifetime users of different categories of pain relievers who met the criteria for the past year abuse or dependence on any pain relievers are shown in parentheses in Table 18 and also presented in Figure 22.

The data indicate that considerable numbers of lifetime users of pain relievers meet the criteria for the substance use disorder. For example, in 2006, about 1.63 million individuals among the lifetime users of any pain relievers met the criteria for the substance use disorder on any pain relievers. Corresponding numbers for the lifetime users of oxycodone products and hydrocodone products categories were 1.01 and 1.23 millions, respectively. About 0.57 million individuals among the lifetime users of OxyContin® met the criteria for substance use disorder on any pain reliever, while about 0.45 million of the lifetime users of oxycodone products other than OxyContin® met the criteria in 2006 (Table 18).

Percentages of lifetime users of any pain relievers with substance use disorder on any pain relievers ranged from 4.4 through 5.1 during 2002 through 2006. Percentages of lifetime users of hydrocodone combination products (range: 5.9% to 7.4%) and oxycodone products (7.3% to 8.6%) with substance use disorder on any pain relievers are higher than those for lifetime users of any pain relievers. Lifetime users of OxyContin® (schedule II) had markedly higher incidence of substance use or dependence disorder on any pain reliever (range: 13.9% to 20.7%) than that of the lifetime users of any pain relievers. Further analysis of data for the lifetime users of oxycodone products other than OxyContin® (schedule II) indicated that users of these products had incidences of substance use disorder (range: 4.1% to 5.8%) that are similar to

those of the lifetime users of any pain relievers and are less than those of the lifetime users of hydrocodone products (Table 18 and Figure 22).

Table 18. Lifetime non-medical users of any pain relievers, hydrocodone combination products, OxyContin®, oxycodone products, and oxycodone products other than OxyContin® and the number of individuals among each of these categories who met the criteria for the past year abuse or dependence on any pain relievers. §

Data Type	Drug Category	Numbers in Thousands (Percentages)*				
		2002	2003	2004	2005	2006
Lifetime Users of	*Any Pain Reliever*	29,611	31,207	31,768	32,692	33,472
	Hydrocodone Combination Products[1,2]	13,952	16,808	17,734	18,875	20,755
	OxyContin®	1,924	2,832	3,072	3,481	4,098
	Oxycodone Products[1,3]	10,151	11,538	11,925	12,029	12,858
	Oxycodone Products Other than OxyContin®	8,227	8,706	8,853	8,548	8,760
Past Year Abuse or Dependence on Any Pain Reliever Among Lifetime Users of	*Any Pain Reliever*	1,509 (5.1)	1,424 (4.6)	1,388 (4.4)	1,546 (4.7)	1,635 (4.9)
	Hydrocodone Combination Products[1,2]	1,042 (7.4)	1,061 (6.3)	1,094 (6.2)	1,210 (6.4)	1,232 (5.9)
	OxyContin®	399 (20.7)	521 (18.4)	514 (16.7)	555 (15.9)	571 (13.9)
	Oxycodone Products[1,3]	876 (8.6)	915 (7.9)	873 (7.3)	985 (8.2)	1,019 (7.9)
	Oxycodone Products Other than OxyContin®	477 (5.8)	394 (4.5)	359 (4.1)	430 (5.0)	448 (5.1)

*Values in parentheses indicate the number of persons in percentages who met DSM-IV criteria for substance abuse or dependence on any pain reliever among lifetime users of specific pain relievers.

[1] Includes other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category.

[2] Includes Vicodin®, Lortab®, or Lorcet®, and hydrocodone.

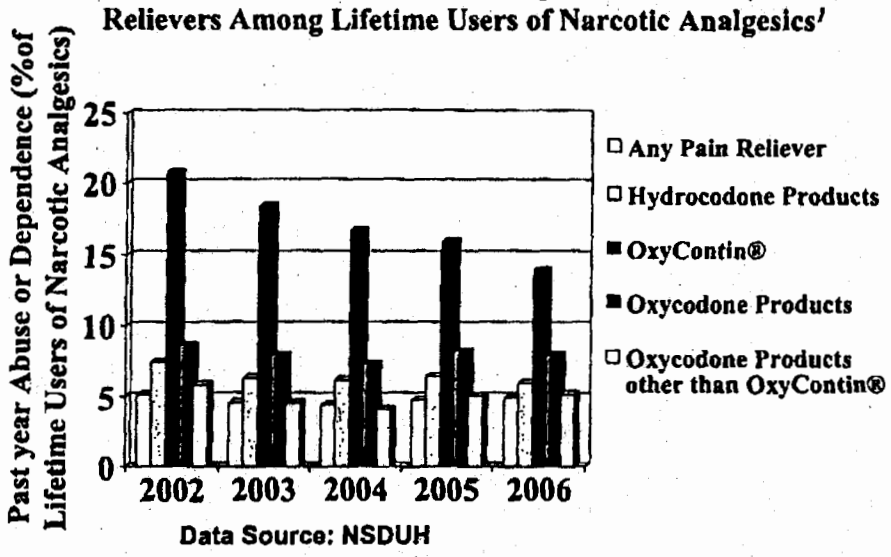
[3] Includes Percocet®, Percodan® or Tylox®, and OxyContin®.

§In the U.S., nearly 100 percent (of total kilogram amounts distributed) of hydrocodone was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone was marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

The above mentioned data suggest that the propensity of the lifetime users of OxyContin® to develop substance use disorder on any pain relievers is markedly higher than that of the lifetime users of any pain relievers (2.8 to 4 fold), hydrocodone products (2.3 to 3 fold), oxycodone products (1.75 to 2.4 fold), and oxycodone products other than OxyContin® (2.7 to 4.1 fold). Lifetime users of oxycodone products other than OxyContin® (i.e., immediate-release single-entity products and immediate-release combination products) are similar to the lifetime users of any pain relievers with regard to their propensity to develop substance use 319

disorder on any pain relievers, but are less (1.5 to 1.8 fold) than that of the lifetime users of hydrocodone products to develop substance use disorder.

Figure 22. Past Year Abuse or Dependence on Any Pain Relievers Among Lifetime Users of Narcotic Analgesics[1]



[1]Oxycodone products include Percocet®, Percodan® or Tylox®, and OxyContin® and other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category. Hydrocodone products include Vicodin®, Lortab®, or Lorcet®, and hydrocodone and other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category.

In summary, these NSDUH data indicate that the dependence potential of hydrocodone combination products is higher than that of oxycodone immediate-release products (schedule II) (i.e., single-entity immediate-release and combination products combined). Therefore, hydrocodone combination products have potential to cause severe psychic or physiological dependence.

7.2.2.2. *Adverse Event Reporting System*

The DHHS review document provided the results of their analysis of Adverse Event Reporting System (AERS) data for abuse/dependence producing properties of hydrocodone combination products and oxycodone products. Using these data, DHHS review document concluded that abuse/dependence ranking for hydrocodone combination products is lower than that of oxycodone products. However, as discussed earlier (see Factor 6), DHHS also cited a number of limitations of AERS database. For example, DHHS stated that AERS case reports cannot be used to calculate incidence reports. Because AERS data is based on voluntary reporting, as acknowledged by the DHHS review, number of factors such as length of time the drug is marketed, the market share, size and sophistication of the sales force, incomplete clinical data, publicity about an adverse reaction and regulatory actions, affect AERS data. As discussed earlier, of particular importance is the marketing approval of OxyContin®, a high dose extended release oxycodone product that had been subsequently subjected to risk management program

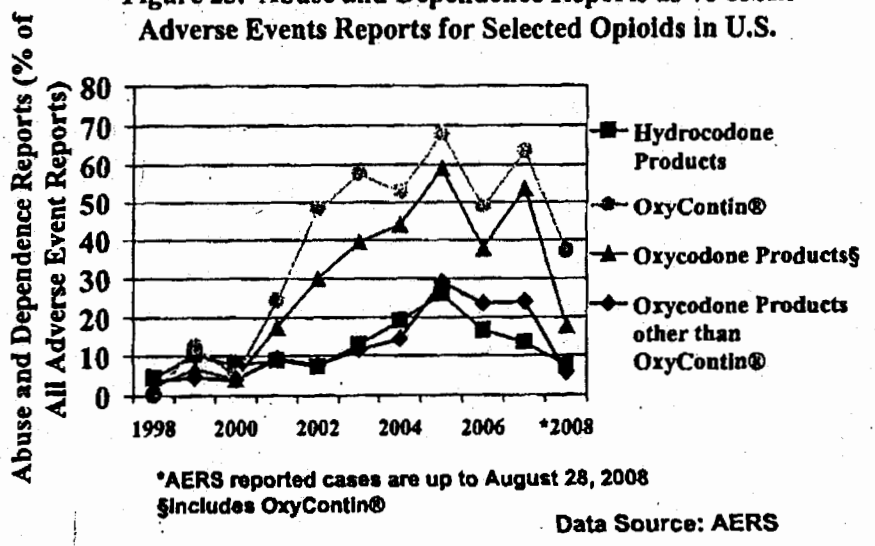
due to concerns about its increasing diversion, abuse and addiction reports.

For the above mentioned reasons and the reasons discussed in Factor 6, DEA calculated the AERS data for oxycodone products other than OxyContin® by subtracting the AERS data for OxyContin® from that of all oxycodone products. Also presented were the data for hydrocodone combination products (see Table 17 in Factor 6). These data were also graphically represented in Figures 20 and 21. According to this analysis, although adverse event reports received from 1969 though August 28, 2008 for all oxycodone products exceeded those for hydrocodone combination products, OxyContin® was mentioned in nearly two thirds of adverse event reports associated with all oxycodone products. Upon exclusion of OxyContin® associated reports, all adverse event reports for the remaining oxycodone products were similar to those for hydrocodone combination products.

Of particular importance is the fact that the abuse and dependence reports associated with hydrocodone combination products expressed as a percentage of its all adverse events (13.3%) was similar to that for oxycodone products other than OxyContin® (13.6%). These are considerably less than the corresponding events reported for OxyContin® (54.9%) (Table 17).

Majority (over 95%) of abuse and dependence events for both hydrocodone combination products and oxycodone products were reported within the last 10 years. Thus, the temporal distribution of annual data of abuse and dependence events reported since 1998 for these products were also presented as percent of the corresponding all adverse event reports for these products in Figure 23. These data show that abuse and dependence events, expressed as percent of all adverse events, associated with OxyContin® markedly increased beginning in 2001 with the peak increases occurring in 2005. The corresponding annual time-course increases for all oxycodone products were similar to, but of slightly smaller magnitude than that for OxyContin®. In contrast, the corresponding increases for hydrocodone combination products and oxycodone products other than OxyContin® were significantly smaller in magnitude as compared to those for OxyContin®. Further, the time-course curves for hydrocodone combination products nearly overlapped with those for oxycodone products other than OxyContin®.

Figure 23. Abuse and Dependence Reports as % of All Adverse Events Reports for Selected Opioids in U.S.



In summary, the above mentioned AERS data analysis suggest that abuse and dependence reports, expressed as percent of all adverse events, for hydrocodone combination products are similar to those for oxycodone products other than OxyContin® and are considerably less than those for OxyContin®.

7.2.2.3. Treatment Episode Data Set

The DHHS review document provided data from the Treatment Episode Data Set (TEDS). TEDS collects data about admissions to drug addiction treatment facilities that receive public funding. According to the DHHS review document, admissions data related to specific drugs is limited. In 2005, there were about 120,000 admissions to treatment where primary, secondary or tertiary substance of abuse was an opioid analgesic. For half of these admissions, narcotic analgesics were the primary substance of abuse. The other half represented dual addictions, such as abuse of opioid analgesics in addition to abuse of another substance such as alcohol or heroin. This is a small fraction of a total of 1.5 million individuals (NSDUH data as mentioned in DHHS review document) who had substance dependence disorder with opioid analgesics in 2005. Further, according to DHHS review document, there were only 11 states that reported data on specific opioid analgesics in treatment admissions and only 3 states reported admissions involving hydrocodone. Further, TEDS does not provide the information from buprenorphine treatment programs. Individuals with prescription opioid analgesics are likely to seek buprenorphine treatment as opposed to opioid treatment programs that report TEDS data.

Further, some product-specific factors also limit the usefulness of TEDS data in quantitatively evaluating the dependence potential of hydrocodone combination products versus oxycodone products for the following reasons. DHHS review document states that the number of opioid analgesic related treatment admissions has been relatively stable between 1995 and 1997, but increased sharply since 1998 with a marked increase in 2001. The beginning of the sharp rise followed the approval of OxyContin®, a high strength extended-release oxycodone product. During the same time period, OxyContin® abuse received widespread media publicity nationwide. Published research reports indicate that among a number of opioid analgesic products, OxyContin® has the most attractiveness for abuse (Butler et al., 2006; Katz et al., 2008).

OxyContin® drug product is marketed in the dose strengths of 10 to 80 mg oxycodone per each dose unit, while hydrocodone combination products are marketed in the dose strengths of 2.5 through 10 mg hydrocodone per each dose unit. Dependence producing properties of a given opioid analgesic is a function of dose. In fact DEA's analysis of drug dependence data obtained from NSDUH suggested that the incidence of substance use disorder is higher among lifetime users of OxyContin®, a high strength extended-release product, as compared to the corresponding data among lifetime users of other oxycodone products (excluding OxyContin® lifetime users) and hydrocodone combination products. TEDS does not provide drug product-specific (e.g., OxyContin®) admissions. Thus TEDS data can not be further analyzed to address this variable.

The above mentioned factors limit the usefulness of TEDS data for performing a quantitative evaluation of dependence potential of hydrocodone combination products versus oxycodone products. Despite these limitations, the fact that both hydrocodone combination products and oxycodone products were mentioned as primary, secondary or tertiary drug of abuse in few states provide a qualitative evidence that the abusers of both these two drug products develop opioid substance use disorder.

7.2.2.4. Published scientific and medical reports

DEA also reviewed various published scientific and medical reports addressing pharmacological properties and addiction to these pharmaceutical opioid products to evaluate the psychic or physiological dependence potential of hydrocodone combination products. These are discussed below

Two recent clinical studies investigated reward related subjective effects of two hydrocodone combination products namely Hycodan® and hydrocodone in combination with acetaminophen (Zacny 2003; Zacny et al., 2005). These studies found that both these hydrocodone combination products produce abuse liability related pleasant effects as well as unpleasant effects that are substantially similar to those produced by μ opioid receptor agonist drug such as morphine. Zacny et al. (2005) reported that acetaminophen, a nonnarcotic active ingredient present in majority (over 90% in kilogram amounts, NPA*Plus*™) of hydrocodone combination products, lacks psychoactive effects in recreational opioid abusers and at therapeutic doses does not produce adverse effects. These data suggest that acetaminophen lacks ability to mitigate the reinforcing effects of hydrocodone.

Similarly, Zacny (2003) showed that Hycodan®, a cough medication containing hydrocodone in combination with homatropine (an atropine-like substance) at two to four times the normal doses produces pleasant (including drug liking) as well as unpleasant subjective effects that are largely similar to the schedule II substance, morphine. This investigator further found that Hycodan®, unlike morphine, decreased "hungry" ratings and heart rate presumably due to homatropine's effects. This investigator stated that the extent to which these effects of homatropine affected the abuse liability related subjective effects measures in their study is not known and further studies are needed to address this issue. However, the decrease in heart rate was mentioned as clinically irrelevant. Therefore, hydrocodone combination products, upon chronic use, similar to its substance, have the potential to cause severe psychic or physiological dependence.

The petitioner provided data regarding patient admissions to his treatment facility and stated that hydrocodone has been frequently mentioned as primary or secondary drug of abuse. According to the petitioner, some patients reported taking up to 70 tablets per day. Majority of the petitioner's patients were initially prescribed hydrocodone in good faith by physicians who were writing prescriptions for pain. The petitioner reported that most of his patients obtained their drugs through doctor-shopping, multiple visits to the emergency room and street purchases. According to Bingle *et al.* (1991) and Giannini (1997), the "medical" addict wittingly receives prescriptions from a licensed physician or dentist for the treatment of acute, sub chronic, or chronic pain. As tolerance to the drug develops the abuser escalates the dose upward. If

cooperative or naive physicians are not available to continue writing the desired prescriptions, the medical addict will forge or steal prescription pads or buy diverted hydrocodone "on the street."

Consistent with the above findings from clinical studies are some recent published reports containing data from epidemiological surveys and retrospective review of medical records of addiction treatment populations (Miller and Greenfeld, 2004; Passik et al., 2006; Rosenblum et al., 2007). Miller and Greenfeld (2004) conducted retrospective review of medical records of all addiction treatment population (534 subjects) admitted and discharged in 2000 from Sparrow/St. Lawrence Addiction Detoxification Unit and found that over 27% (144 subjects) were dependent on prescription opioid medications. Among the prescription opioid dependent subjects, Vicodin was the most frequently mentioned drug (53% of the users) followed by OxyContin (19% of the users).

Passik *et al.* (2006) conducted a survey of 109 prescription drug abusers entering a treatment facility in central Kentucky situated in a location in a part of the county known for prescription opioid, more specifically OxyContin®, abuse. These authors found that the percentage of participants reported abusing hydrocodone were the highest (75%) followed by oxycodone-containing products (69%). When asked about the preference, oxycodone extended-release product, OxyContin®, had the highest preference for abuse (n=65; 60%), followed by Lortab (n=40; 37%), Percocet (n=15; 14%), methadone (n=7; 6%), morphine (n=4; 4%), Lorcet (n=3; 3%), Duragesic (n=3; 3%), Dilaudid (n=2; 2%), Vicodin® (n=1; 1%) and Tylenol #3 (n=1; 1%). Majority of respondents who reported abusing OxyContin® (n = 63/65), Lortab (n= 24/40) or Percocet (n= 12/15) had altered delivery system of the prescription drug by chewing, snorting, or using intravenous administration.

Rosenblum et al. (2007) conducted multi-state (33 states) survey of 5,563 opioid-dependent persons enrolling 72 methadone maintenance treatment programs to determine the prevalence of prescription opioid abuse, factors associated with prescription opioid abuse and sources for prescription opioids. Regions with high prevalence of prescription opioid abuse were over sampled for this survey. These authors defined primary opioid as the opioid drug that is used the most before coming to the methadone maintenance treatment programs. These investigators found that the prevalence of abuse of heroin and prescription opioids with in the past 30 days were 59% and 67% of the total respondents, respectively. The lifetime prevalence was 70% for heroin and 83% for prescription opioids. Thirty-eight percent reported prescription opioid as the primary drug while 53% reported heroin. Among primary prescription opioid abusers, lifetime prevalence of abuse of oxycodone (89% for controlled release products and 81% for immediate-release products) and hydrocodone (88%) was high followed by morphine (59%), methadone (58%) and heroin (33%). Similarly among the primary prescription opioid abusers, the most frequently abused prescription opioids in the past 30 days were controlled release oxycodone (71%), and hydrocodone (67%) followed by immediate-release oxycodone (59%), methadone (40%) and heroin (13%). One-third of primary prescription opioid abusers reported a history of injecting their primary drug.

Rosenblum et al. (2007) also found that among primary heroin abusers, the lifetime and past 30 day prevalence of abuse of prescription opioids were 69% and 39%, respectively. The

most frequently abused prescription opioid during the past 30 days were hydrocodone (16%), methadone (16%), controlled release oxycodone (15%) and immediate-release oxycodone (13%). Among primary prescription opioid abusers the most frequently cited primary opioids were controlled release oxycodone (47.4%) and hydrocodone (24%) followed by methadone (8.2%) and immediate-release oxycodone (7.1%), morphine (6.3%), hydromorphone (5.1%), fentanyl (0.9%), other opioid (0.8%) and buprenorphine (0.1%). These data indicate that hydrocodone products are about 3.5-fold more likely than immediate-release oxycodone products to be mentioned as the primary drug of abuse in these prescription opioid dependent subjects.

The above mentioned epidemiological data are consistent with the data from NSDUH and AERS databases and from clinical studies that hydrocodone, similar to oxycodone, has potential to cause severe psychic or physiological dependence. Nonnarcotic active ingredients present in currently marketed hydrocodone combinations products do not deter hydrocodone's potential to cause severe psychic or physiological dependence.

Summary

Pharmacological similarities between hydrocodone and schedule II opioid analgesics such as morphine, oxycodone and hydromorphone, strongly indicate that hydrocodone substance has a high potential for abuse and to cause severe psychic or physiological dependence. The data provided in Factor 1 and the data provided herein suggest that hydrocodone combination products, similar to its substance, have potential to cause severe psychic or physiological dependence.

8. WHETHER THE SUBSTANCE IS AN IMMEDIATE PRECURSOR OF A SUBSTANCE ALREADY CONTROLLED UNDER THIS SUBCHAPTER

Hydrocodone-combination products are not immediate precursors of any substance controlled under the CSA, as defined in 21 U.S.C 811(e).

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Appendix 1

Abridged DEA Case Reports

(A random sampling of cases intended to show different types of diversion)

[redacted]

A female pharmacy technician was arrested for hydrocodone diversion. Using her cell phone the individual was calling in bogus prescriptions from a number of local pharmacies for personal use.

[redacted]

A female was arrested for fraudulently obtaining prescriptions utilizing her physician's DEA registration number and bogus "phone-in" prescriptions.

[redacted]

A pharmacist was arrested after a five month investigation for running a large scale internet pharmacy business and mail order pharmacy. The pharmacist diverted 300,000 dosage units of hydrocodone (among others) over a two year period. No valid prescriptions or physicians were utilized.

[redacted]

A male registered pharmacist was arrested for fraudulently filing fake prescriptions for 8,570 dosage units of hydrocodone.

[redacted]

A physician was indicted for writing hydrocodone prescriptions (among others) for other than legitimate medical purposes. Prescriptions for over 42,835 dosage units were written for other than legitimate medical purposes and were being illegally distributed through street sales.

[redacted]

A male physician was arrested for delivery of hydrocodone (570 dosage units of Vicodin ES) to patients with no medical complaint. Four separate purchases were monitored.

[redacted]

A female registered nurse was arrested for illegal distribution of hydrocodone. The nurse was removing hydrocodone from the intensive care unit and selling them out of her home.

[redacted]

A male pharmacist was arrested for delivery of hydrocodone without a valid prescription. Two purchases were witnessed of 160 dosage units and 400 dosage units, respectively.

A male veterinarian was arrested and voluntarily surrendered his DEA registration for ordering approximately 20,000 dosage units of hydrocodone and 249 bottles of hydrocodone syrup for personal use. The veterinarian admitted to consuming 65 tablets of hydrocodone per day.

A male physician was arrested for distributing hydrocodone from his office for no known medical reason. Most of the prescriptions written by the doctor were averaging 60 to 120 tablets per day per patient. The physician was averaging over 600 prescriptions per day. In one case he had written 39,281 dosage units for one patient.

A male dentist was arrested in a "sex for drugs" scheme with area "exotic dancers" and for self-abusing the hydrocodone, himself.

A female physician was arrested for obtaining hydrocodone (among others) for personal use. The doctor was writing prescriptions utilizing names of family members to obtain the opioid. The doctor had concealed the drug use from her own physician who was treating her for lupus at the time.

A female licensed practical nurse was arrested for ordering hydrocodone for personal use utilizing the clinics DEA registration number. A large cache of opened and unopened bottles were found in the nurse's locker and at her home.

A female office manager for a local physician was arrested for purchasing 16,300 dosage units of hydrocodone during a one year period. The manager was utilizing the physician's DEA registration number to order the drugs for delivery to the office and forging the physician's checks to pay for the drug delivery. The drugs were reportedly for personal use.

A male pharmacist was arrested for delivering 1,976 dosage units of hydrocodone to a local street level drug trafficker. The drug cache was intercepted. Seizure of the pharmacist's car revealed another 995 dosage units of hydrocodone.

A nurse practitioner was arrested for using her power of authority at the physician's office to coerce office assistants into calling in prescriptions for hydrocodone for her without the knowledge of the physician. Patient names or family members' names were used and the nurse practitioner would pick the drugs up at the pharmacy for personal use.

A female was arrested for bogus "phone-in" prescriptions of hydrocodone for personal use.

A female pharmacy technician was arrested for passing forged prescriptions for hydrocodone. The woman stated that she was addicted to the drug and had stolen a prescription pad from an area physician. The technician was on bail from a previous arrest for similar forging of prescriptions for hydrocodone.

An owner of a group of weight loss clinics was arrested for employing physician interns to utilize their DEA registration numbers to dispense controlled substances. The owner was having physicians register at the clinics while none of the interns were licensed by the State of Louisiana to dispense controlled substances. The owner was in personal possession of 1,590 dosage units of hydrocodone (among others). A search of the owner's home revealed another 14,928 dosage units of hydrocodone (among others). The owner was distributing the drugs for street sales.

A male pharmacist was arrested for stealing over 10,000 dosage units of hydrocodone (among others) over a 14 month period.

A male pharmacist was arrested for illegally obtaining hydrocodone by use of stolen prescription pads from three physicians in the area.

A male physician was arrested for illegally obtaining hydrocodone by using bogus prescriptions written for a 92 year old patient residing in an assigned living center. The doctor admitted self use of the hydrocodone. At the time, the physician was 'chief of staff' at the University of Arizona Medical Center.

A male pharmacist and owner of a pharmacy in the Houston area pled guilty to illegal delivery of hydrocodone. He was considered Houston's most prolific diverter of hydrocodone and the 8th largest volume hydrocodone purchaser in the United States.

A male high school teacher was arrested for selling hydrocodone to students for grades or sexual favors. The teacher acquired controlled substances by fraud, elderly abuse, and theft.

A male registered nurse was arrested for stealing and selling hydrocodone. The nurse admitted to taking half of the controlled substances designated for patients use in the intensive care unit. He stockpiled the tabs for future sale from his home.

A female pharmacist was arrested for personal abuse of over 70,000 milliliters and 1,000 tablets containing hydrocodone. The pharmacist would pay the token co-payment of prescriptions written for other patrons and use the drugs herself.

A female dental office assistant was arrested for fraudulent "phone-in" prescriptions in the name of some of the dentists' patients and picking them up for her own use.

A veterinarian was arrested for writing and acquiring prescriptions for hydrocodone which was being used by his addicted brother-in-law.

A male attorney was arrested for fraudulently writing prescriptions and acquiring the hydrocodone at pharmacies. The attorney ordered over 20,000 dosage units on 18 different occasions without the knowledge of his physician client.

A male physician was arrested for writing over 5,500 fraudulent prescriptions, totaling over 302,500 dosage units. Video taped evidence showed that the physician was providing prescriptions in exchange for sexual favors.

A male pharmacist was arrested for diverting and selling hydrocodone over a two year period. Two hundred hydrocodone tabs were sold for $750 on several occasions.

A male physician was arrested after writing hydrocodone prescriptions for no legitimate medical reason during a series of undercover purchases.

A physician and two pharmacists were arrested for fraudulent Medicare claims for treatment of non-existent conditions for the purpose of obtaining hydrocodone for sale. Multiple undercover purchases were made.

A male physician and attorney was arrested for selling over 5,000 dosage units per month of hydrocodone and other controlled substances. Approximately 40,000 dosage units were seized at the home along with $90,000 dollars in proceeds.

A male was indicted on 27 counts for obtaining over 2,500 dosage units of hydrocodone by traveling around the states of N.C., S.C., and GA and obtaining prescriptions under false pretenses from physicians and hospitals for the same "medical complaint". The drugs were intended for subsequent sale.

A physician and eight others were arrested for an estimated 15 million dollar health care scheme for writing postdated prescriptions for hydrocodone and mailing them to other individuals.

A male dentist pled guilty of misrepresentation and diversion of hydrocodone. The physician was writing prescriptions after revocation of his license to practice. He dispensed prescriptions for over 3,000 dosage units of hydrocodone for his own reported back and leg pain.

A female was arrested at a pharmacy after paying for two fraudulent prescriptions. The female was using a prescription pad she stole from her doctor's office to write prescriptions for her addiction to Vicodin.

Four individuals were arrested for selling hydrocodone which they obtained from prescriptions received at a neurology and pain clinic and were found selling the tablets in the parking lot of the facility.

The assistant director of an "impaired physician's program at a major hospital in Chicago surrendered his DEA registration after being arrested for falsely prescribing Vicodin for his addiction to the drug.

A male pharmacy technician was arrested for diverting over 130,000 dosage units of Vicodin.

A male physician was arrested for fraudulently prescribing hydrocodone in a "sex for drugs" scheme. The physician provided 5 prescriptions of hydrocodone, 100 tablets per Rx, in two different names to an undercover agent.

A female pharmacy technician was arrested for diverting hydrocodone from her employer.

A male pharmacy technician was arrested after video tapes showed him diverting hydrocodone for personal use. The pharmacy had already reported a loss of over 130,000 dosage units prior to this single arrest.

A male was arrested for intimidating an elderly physician into writing prescriptions for hydrocodone for his personal use.

A male pharmacy technician was convicted of diverting hydrocodone. The technician was ordering extra bottles of stock for personal sale for profit.

A female office manager for a physician turned herself into authorities after discovery of diversion of over 900 dosage units of hydrocodone (Vicodin) and over 100 dosage units of Lorcet for personal use.

A physician surrendered his DEA registration after being discovered of calling in prescriptions for hydrocodone "day after day". The prescriptions were dispensed in his wife's name. The daily prescription was for 30 to 40 tablets a day. The physician would pick up the prescriptions without his wife's knowledge. The physician admitted to having a "30 pill a day habit."

A female registered nurse was arrested for fraudulent "phone in" prescriptions for hydrocodone from eight different pharmacies. The drugs were reported to be for "personal use".

A female was arrested for fraudulently receiving in excess of 130 prescriptions, primarily hydrocodone, over a 6 month period.

A pharmacy technician was arrested for stealing in excess of 900 dosage units from the pharmacy.

A registered pharmacist was arrested for illegally distributing hydrocodone to his girlfriend. A search warrant to her apartment revealed numerous bottles with the names of various customers at the pharmacy. The case was based on sex for drugs.

A pharmacist was arrested for illegally distributing hydrocodone with intent to sell more than 500 g or more of the drug. He was distributing the drugs via the mail and Faxed prescriptions he knew were fraudulent.

A female pharmacy technician was arrested for stealing stock bottles of hydrocodone (among others) during a three week period. She sold them for $7 and $10 per tablet.

A dentist was indicted for misrepresentation and fraud for obtaining hydrocodone in other people's names for his own use. The dentist was using a stolen prescription pad taken from a physician colleague in the same office complex.

A male suspect was arrested for making a fraudulent prescription on his computer. He forged his doctor's signature and made out the prescription for his sister.

A female pharmacist confessed to diverting 150 to 200 dosage units of hydrocodone from Eckerd Drugs. The pharmacist diverted over 30,000 dosage units over a one year period.

Two criminal complaints were filed against two individuals for diverting hydrocodone from a pharmacy. A total of 37,000 dosage units were diverted in a 6 month period.

A pharmacy technician was arrested for dispensing hydrocodone without prescriptions. The technician would remove stock bottles from the shelf when she believed no one else was looking and sold them in the parking lot outside the pharmacy.

An owner of a pharmacy was arrested for sale of over 500 g of hydrocodone and intent to illegally sell the drug via the postal system.

A registered pharmacist was arrested for theft and diversion of hydrocodone from his pharmacy.

A federal jury convicted a physician for illegal distribution of drugs including hydrocodone.

A medical office assistant was arrested and admitted to fraudulently "phoning in" prescriptions for hydrocodone on five separate occasions.

An unemployed housewife was arrested and admitted to fraudulently "phoning-in" prescriptions for hydrocodone for both herself and her husband.

A male pharmacy technician was arrested for fraudulently prescribing hydrocodone on three separate occasions. The pharmacy tech used the DEA registration number of his ex-physician.

A male physician was arrested and charged with 2 counts of illegal distribution of a controlled substance without a legitimate medical reason. During the short period of the investigation the physician was responsible for diverting hundreds of dosage units of hydrocodone. The physician voluntarily surrendered his DEA license and prescription privileges at the time of his arrest.

Two male suspects were arrested for using doctor's names and DEA numbers to fraudulently obtain hundreds of dosage units of hydrocodone and other scheduled drugs from pharmacies, then using and distributing the controlled drugs to friends and associates. The two were charged with 13 counts of obtaining controlled substances by fraud

A male registered nurse, employed at the Veteran's Hospital, was arrested for knowingly acquiring possession of at least 350 tablets of hydrocodone as well as other drugs for his personal use.

A female was arrested and charged with twenty counts of obtaining controlled substances by fraud, mostly hydrocodone. The female posted bond and was released on bail. While out on bail the DEA offices received information that the same female was using a physician's DEA registration number to obtain hydrocodone; while on bail from the original charges, the female had obtained an additional 240 dosage units of hydrocodone fraudulently by phone-in prescriptions

An investigation into the prescription practices of a medical doctor was initiated when the DEA was notified that the physician had been providing hydrocodone and alprazolam to an individual in exchange for sex. Under consensual telephone calls, the physician stated he was creating patient charts for individuals and falsifying laboratory work to complete the charts. During the investigation another individual was found who was providing the doctor with sex for hydrocodone. The physician had written prescriptions for approx. 312,000 tabs of hydrocodone and had purchases at least 8,000 tablets of hydrocodone from pharmaceutical distributors. Local prices of hydrocodone are $10 to $15 per tablet which could have yielded 3.2 to 4.8 million dollars.

A male physician was interviewed by DEA regarding prescription errors. During the interview the doctor confessed to writing prescriptions for three employees who would return the drugs to the doctor for his own personal use. He surrendered himself and his DEA registration to the investigators. The Denver office placed a code "1" on the DEA registration number. Charges are pending in Denver.

A female was arrested for posing as a nurse practitioner and utilizing a doctor's registration number to receive fraudulent prescriptions of Vicodin.

A male anesthesiologist from the University Health Sciences Center was arrested after he consented to a search of his home and two vehicles and the discovery of a number of controlled substances, including hydrocodone, were found. The doctor surrendered his DEA registration number and confessed to providing controlled substances to friends, family and neighbors without legitimate medical need. Charges are pending.

A male physician was charged with 14 counts of drug-related crimes; three counts of distributing hydrocodone cough syrup and Tylenol #4's, distributing Valium for non-medical purposes; and 11 counts of omitting material on required records.

A male registered pharmacist was arrested for unlawful distribution and dispensing of hydrocodone. A juvenile was interviewed after arrest for selling hydrocodone to other high school students. The juvenile worked at the K-mart where the pharmacist worked. Over a ten month period the pharmacist could not account for 1,766 hydrocodone tablets, 54 methadone tabs, 80 Ritalin tabs, and 144 Lortabs. The pharmacist confessed to distributing only 3 codeine tabs to co-workers to treat pain without the authorization of a physician. He also confessed to distributing drugs to co-workers by issuing prescriptions in his name, passing them through his insurance and splitting the prescriptions with his co-workers.

The chief pharmacist at a local hospital was arrested for possession of hydrocodone and for dispensing controlled substances without prescriptions. A 16 month audit revealed shortages of 4,400 dosage units of hydrocodone (7.5 Lortab), 4,600 Tylenol #4's, and 100 dosage units of Vicodin. A 42 month audit revealed that an additional 1,770 Lortab and 1,453 Tylenol #4's may have been diverted.

A husband and wife were arrested for possession and intent to distribute controlled substances. The female was working as a pharmacy technician and was arrested leaving the pharmacy with hydrocodone, Lortab, and Viagra. She was previously fired from a hospital pharmacy for similar offenses. She confessed to selling the drugs for profit. Her husband was arrested at their home after a warrant was executed. Numerous drugs were found in the home.

A physician was arrested for writing excessive amounts of controlled substances, primarily hydromorphone and hydrocodone. Undercover officers obtained prescriptions without presenting any medical complaint. As detailed in the medical record, the hydrocodone was prescribed "because the patient asked for it and it made him feel good". The physician has surrendered his DEA license. The owner of the medical center also wrote prescriptions on this physicians DEA number and is being investigated for Medicaid fraud and diversion, as well.

A physician and his wife were arrested for illegally distributing hydrocodone. The physician's DEA registration was revoked at the time of the distribution. He was prescribing Vicodin for family members, his wife would pick up the prescriptions, without the family members knowledge.

A registered pharmacist was arrested for possession and diversion of HC-tussive (hydrocodone) from a large chain pharmacy where he worked.

A male physician was arrested and subsequently lost his DEA license for writing prescriptions for money. Fifteen prescriptions were purchased by an undercover agent for $500. Other agents purchased 10 additional prescriptions for $400.

A male physician surrendered to officials for arrest on drug charges. The physician and three others ran a city weight clinic and diverted thousands of dosage units of Vicodin, Didrex, and methadone from the clinic. The physician pled guilty to two counts and surrendered his license. Two co-defendants, a physician and ex-police officer are expected to enter similar pleas in the next few weeks.

An owner and sole pharmacist at a local drug store was arrested on 8 counts of unlawful possession with intent to distribute and 8 counts of intentionally omitting material information from required records. The pharmacist was selling large amounts of controlled substances. Under a reported threat of harm, the pharmacist stated he was being blackmailed to distribute drugs to one individual. The indictment charges that the pharmacist distributed in excess of 11,855 Vicodin/Vicodin ES (among other drugs) over a five year span. The "blackmail" excuse is being investigated but it is reported to contain many discrepancies.

A man was arrested for forgery, possession of a controlled substance, and diversion of prescriptions (among others). The man was a long time companion of a physician and was forging prescriptions to obtain controlled substances for a protracted time, even after the physician had died. The prescriptions included Vicodin, Percocet, Didrex, Seconal, and carisoprodol.

A psychiatrist signed a memorandum of agreement to pay a $12,500 fine for knowingly prescribing inappropriate amounts of controlled substances to known addicts. Under the guise of running a pain management clinic the psychiatrist was supplying large amounts of Vicodin, Percocet, and Dilaudid to known addicts.

A male physician was arrested for writing a series of prescriptions for himself using other individual names and addresses (patients of his). He used his own phone number and physician's name.

A registered pharmacist was arrested for unlawful dispensation of hydrocodone. The pharmacist

was using hydrocodone for payment to a janitor for cleaning services in the pharmacy. After being charged the pharmacist contacted one of the witnesses in an attempt him to change his testimony (witness tampering)

A female medical assistant was arrested for fraudulently obtaining hydrocodone through bogus "call-in" prescriptions to a local pharmacy using her ex-employer's DEA registration number. State charges were filed.

Federal indictments were set down on an osteopathic physician after a nine year investigation. Seven counts involved the illicit dispensing of drugs, including hydrocodone. The IRS found the doctor's wealth to be several million dollars; the locations of his practice were so unclean and vermin infested that the facilities were immediately closed by a health representative.

A 47 yr old male was arrested for writing and processing forged prescriptions for hydrocodone tablets from a prescription pad at his family physician's office. The physician was unaware of the diversion. Local charges were filed.

During an interview regarding a loss of 50 pints of hydrocodone/homatropine syrup, a pharmacist admitted to DEA agents of diverting the substance for personal use. State charges were filed.

A pharmacy technician was arrested outside of a Walmart store and charged with two counts of possession with intent to sell controlled substances and one count of felony retail theft. The young lady was video-taped removing medications from the pharmacy. From January 01 to 23 March the pharmacy tech had made three orders for hydrocodone from the manufacturer and had diverted 10-12 bottles of hydrocodone products (especially Lorcet 10/650).

DEA received intelligence that a 54 yr old male was a major distributor of hydrocodone in Broward and Palm Beach counties. The individual was arrested upon delivering 5 sealed bottles of hydrocodone (2,500 tablets) to an undercover agent. A search of the individual's vehicle revealed two additional sealed bottles of hydrocodone (1,000 tablets) and Xanax (1,000 tablets). During December an undercover agent had purchased three other sealed bottles of hydrocodone (1,500 tablets); one bottle was labeled and local offices are tracing the diversion from the provided information. This case involves a total of 5,000 hydrocodone tablets.

A male physician was indicted by a grand-jury for knowingly or intentionally refuse or fail to make, keep or furnish any record, notification, order form, statement invoice or information required under the CSA, namely by receiving and dispensing controlled dangerous substances unlawfully. A review of purchases established that the physician purchased a total of 39,144

tablets of hydrocodone (Lorcet) and a benzodiazepine (Lorazepam) and their generic equivalents (Lortab 10 mg: 17,244; hydrocodone 7.5: 200; Lorcet + 7.5: 100; Vicodin ES, 7.5: 600). The doctor could not produce any records for the receipt or the distribution of those controlled substances; nor could he tell the investigators what happened to those substances.

A male and female were arrested and charged with four counts of possession of hydrocodone and eleven counts of Medicaid fraud. The male would call in "bogus" prescriptions pretending to be a physician and the friend would pick up the prescriptions and sell them to a third party. The prescriptions were being charged to Medicaid funds.

A medical assistant was arrested for illegally obtaining several prescriptions of 10mg hydrocodone + APAP tablets in patients names and having them delivered to the doctor's office or picking them up without the patient or doctor being aware of the prescription. The prescriptions were unwittingly charged to the patient's insurance company by the pharmacist.

A male physician was arrested after the doctor purchased and received 100 hydrocodone-containing tablets (Lorcet) from a prescription of a confidential source which the doctor was using for himself. Over a 10 month period the source had purchased 18 prescriptions for the doctor which including hydrocodone (Lorcet & Tussionex) and other pain (Percocet) and anxiolytic medications (Xanax & Valium). The lawyer representing the physician told local DEA agents that the physician would surrender his medical and DEA registration licenses immediately.

Two drug companies notified the DEA that a physician had ordered and received **150,000** tablets of hydrocodone in one month. The physician notified the FBI in Las Vegas when he discovered that his brother and an accomplice were using his DEA registration number to order drugs. The two ordered hydrocodone, anabolic steroids, and diazepam from drug companies. The drugs would be delivered to the physician's address to be picked up by the brother without the physician's awareness. They would be transported to California, packaged in small bags and shipped to an associate in Boston or in Laguna Nigel, CA. The brother was arrested; the physician has been cooperative and is believed not to be involved.

As part of a two year investigation warrants were served on a pharmacy to collect evidence against the pharmacist who had been suspected of improperly distributing controlled substances, including hydrocodone. The pharmacist would order by telephone "excessive" amounts of controlled substances, knowingly receive fraudulent prescriptions from street dealers and accept cash and electronic equipment for the purchases. The pharmacist also defrauded Medicaid. During a 10 month period, the pharmacist purchased and delivered 444 gallons of Tussionex. The search warrant uncovered counterfeiting evidence and the secret service was brought into the case, as well.

The diversion office received a letter from a pharmacy to report the termination of an employee for generating new controlled substance prescriptions for a patient without a physician's authorization. A total of 690 hydrocodone tablets were illegally dispensed over a period of 3 months using this technique. The pharmacy tech also deleted prescriptions from the computer files; 11 prescriptions totaling 440 tablets of hydrocodone were deleted from the files. An additional 7 prescriptions totaling 300 tablets was also discovered.

A 40 yr old male dental equipment repairman was obtaining various dentists' DEA registration numbers and patient information when he arrived at the offices to repair equipment. He called in prescriptions of hydrocodone and then poses as the patient using the information he picked up at the dentist offices. The individual was arrested during a purchase at a local drug store.

An ongoing investigation of a female who habitually uses bogus "call-in" prescriptions to obtain hydrocodone. This individual obtained at least 575 tablets of hydrocodone containing products (Vicodin, Lortab) from different pharmacies by using different physician's names and bogus prescriptions.

A 34 yr. old female was using a number of aliases under which she would use "call-in" orders from different physicians in the area. The suspect used a number of drug stores in the area to obtain hydrocodone by fraud.

An 18 yr old female pharmacy technician admitted to and was arrested for supplying hydrocodone to her sister's boyfriend without a prescription. The pharmacy tech would remove prescriptions from a pile of prepared prescriptions waiting to be picked up; she would have her friend drive by the 'drive-through' window and pass it to him. When the legitimate customer would come by to pick up their prescription she would search for it, notify the pharmacist it was not there, and they would re-issue the legitimate prescription to its rightful owner.

A former medical assistant (MA) to a registered physician was arrested for illegally obtaining the doctor's prescription pad. The MA wrote prescriptions for a male accomplice for hydrocodone. The MA used the physician's name and stamp signature. The MA admitted to writing two fraudulent prescriptions for her accomplice. Pharmacy records showed that four additional prescriptions were forged and processed dispensing a total of 520 hydrocodone tablets during a 3 month period. The MA was taken into custody after a bond reduction hearing for 1 count of trafficking hydrocodone. Through false prescriptions she fraudulently obtained, among others, 900 dosage-units of hydrocodone.

A female registered nurse was arrested for two counts of prescription forgery (state charges) which included hydrocodone. She was confronted by authorities and was found to have controlled substances in her possession in her purse including prescriptions for hydrocodone. The RN admitted to forging the prescriptions. She was released on bail and will be arraigned at a later date.

A male was arrested and charged with distribution of hydrocodone. On two occasions the individual sold stolen hydrocodone to a cooperative source. A subsequent search warrant resulted in seizure of 40 hydrocodone tablets, marijuana, money, a gun, and paraphernalia.

A veterinarian was arraigned on ten counts of obtaining possession of a controlled substance, hydrocodone, by misrepresentation, fraud, forgery, deception and subterfuge by writing prescriptions in the names of his animal patients. This investigation is ongoing.

A young female registered nurse was arrested on 13 counts of obtaining a controlled substance (hydrocodone) by fraud. This individual used "call-ins" to order prescriptions from a local Walgreen's pharmacy using a local physician's name and DEA registration number. A total of 180 tablets and 540 mls of hydrocodone containing products were illegally obtained by the RN over a two month period.

A pharmacy manager was indicted on one count of unlawfully, intentionally, and knowingly delivering a dangerous drug, hydrocodone, to special agent of the DEA. He pled no contest and was sentenced to one year suspended sentence, two years probation, and $300.00 fine.

A male veterinarian was indicted on three counts of obtaining controlled substances by fraud. The individual is not a currently licensed veterinarian in the state of Tennessee nor has he a DEA registration. The case was processed through a state indictment after the US attorney's office declined the case.

A dentist and his wife were arrested on 27 counts of obtaining Vicoprofen by fraud (among other charges). The dentist had previously surrendered his DEA registration for prescribing medications to himself and his wife for no medical purpose. The dentist was using his partner's DEA registration.

A doctor confessed to diverting quantities of hydrocodone for his own personal use from patients for a period of over one year. The doctor surrendered his registration and entered a no contest plea and was sentenced to 60 months state probation, $900 court costs, $2500 reparation fee, and 1,000 hours community service.

A female office manager at a doctor's office was arrested and charged with on count of hydrocodone possession (among others). The office manager utilized the doctor's prescriptions throughout the county. The elderly doctor was "being taken advantage" of by his live-in office manager. Additional charges are contemplated.

A male pharmacist technician was arrested for diversion of 4,500 dosage units of hydrocodone.

Two individuals were arrested for Vicodin associated diversions. One female was arrested for obtaining Vicodin by fraud, by using her ex-husbands registration number to obtain the drug. The pharmacist, who had been notified by the first individual's spouse that the prescriptions were not authorized and she continued to fill them. Both individuals were arrested.

A physician and a pharmacist were arrested for supplying controlled substances outside the realm of medical treatment. NDI investigators made 13 undercover purchases of prescriptions for hydrocodone products and other controlled substances. The physician owned the pharmacy and would provide prescriptions that he told the patients to fill at the family pharmacy.

A pharmacy technician was arrested for distribution of oxycodone (SCH II) and hydrocodone (SCH III) on three occasions

A woman was sentenced for illegally obtaining approximately 6,000 dosage units of hydrocodone by fraud.

A male pled guilty to two state counts of illegally obtaining Vicodin tablets by fraud and deceit. The individual called physicians in the area and claimed to be a dentist. He stated that a family member was in town and in need of pain medication until they could visit the doctor's office. The defendant allegedly obtained nearly 3,000 tablets by using the telephone to deceive 80 physicians in the New Orleans area.

A medical doctor pled guilty and was sentenced for distribution of Dexedrine, Percodan, Vicodin ES and Valium. The prescriptions were issued outside the course of the usual practice of medicine and failed to keep complete medical records on the recipients of the prescriptions.

A physician was found guilty of 19 counts of unlawful distribution of Percocet (oxycodone) and 9 counts of unlawful distribution of hydrocodone (Lorcet and Vicodin) and benzphetamine (Didrex). The physician continued to prescribe medications even after surrendering her DEA registration.

A pharmacist and owner of a pharmacy were indicted on 7 counts. One count was for the distribution and dispensing of hydrocodone for other than legitimate medical purposes and outside the scope of professional practice near a school. Earlier, this same individual was arrested for illegal possession and distribution of a controlled substance.

A woman posing as a doctor's medical assistant was arrested on one count of unlawful acquisition of hydrocodone.

A medical doctor was arrested for state charges of obtaining hydrocodone, a controlled substance, by deception. The doctor had previously admitted diverting quantities of hydrocodone for his own personal use from patients for a period of over one year.

An individual pled guilty to one count of prescription forgery (120 forged prescriptions authorizing 190 refills for hydrocodone (Vicodin) and Klonopin). The diversion involved in excess of 3,000 dosage units.

A federal search warrant was served on a pharmacy in Murrysville, PA. Also served was a DEA Immediate Suspension of the pharmacy's registration. The pharmacy had been suspected of "large scale" diversion of hydrocodone (and alprazolam). An estimated 3,000 dosage units of Vicodin were diverted and approx. 20 other arrests are pending.

A dentist was found guilty of 8 counts of felony distribution. Vicodin-ES and Lorcet (both hydrocodone) were prescribed to cooperating patients/drug users who would pass the prescriptions on to pharmacies and then return to split the drugs with the dentist.

A registered pharmacist and owner of a pharmacy were sentenced for the illegal sale of 100 Vicodin (hydrocodone) tablets.

An individual pled guilty to diverting in excess of 7,000 dosage units of hydrocodone by use of falsified prescriptions

A licensed practical nurse (LPN) was arrested for ordering "phone-in" prescriptions in the amount of approximately 1200 dosage units of hydrocodone and phentermine. The LPN used the DEA registration number of her employer. The controlled substances were purchased for personal use and for the use of the LPN's daughter.

A registered pharmacist confessed to, and was subsequently arrested for, the diversion of 1,000 dosage units of hydrocodone. The hydrocodone was illegally dispensed in exchange for cocaine and "favors". The drugs were dispensed without a prescription.

A physician was convicted and sentenced for fraudulently obtaining in excess of 7,000 dosage units of Percocet and in excess of 53,000 dosage units of Vicodin (hydrocodone) for personal use.

A man pled guilty to knowingly and intentionally using the DEA registration number of his wife, a medical doctor, to obtain Lorcet (hydrocodone).

A 257 count federal grand jury indictment was handed down for a pharmacy owner for diverting thousands of dosage units of Hycodan® and Alexsia (both hydrocodone). 15 associated defendants were also charged in the indictment. During the commission of the search warrant a number of unlisted individuals entered the pharmacy with fraudulent prescriptions to be filled; all were subsequently arrested.

A pharmacy technician was arrested after being caught on video tape stealing 100 tabs of Vicodin (hydrocodone).

A woman pled guilty for possession with intent to distribute hydrocodone. The woman was an employee of a pharmacy. An accountability audit covering 8 months was conducted and revealed shortages of 10,775 hydrocodone tablets.

A federal grand jury returned an indictment of a medical doctor for enlisting and/or manipulating several individuals into assisting him in filling bogus prescriptions. Using in excess of 18 different pharmacies, the doctor obtained in excess of 1500 dosage units of Percocet and Lortab (hydrocodone) without legitimate medical purposes.

A medical doctor was sentenced for possession of an excess of 15,000 dosage units of hydrocodone.

A medical doctor was convicted of knowingly and intentionally distributing 298 prescriptions for Vicodin ES (hydrocodone) without a legitimate medical reason. The prescription contributed to the death of a patient.

A doctor of osteopathy was indicted for using a DEA registration number belonging to another physician (his employer) to obtain Lortab and Tussionex (hydrocodone) for his personal consumption. He allegedly distributed a portion of the controlled substances.

A woman was arrested on 11 counts of obtaining controlled substances. The woman received in excess of 12,000 dosage units of Vicodin (hydrocodone), Darvocet, and Xanax without legitimate prescriptions. Investigators discovered that in a nine month period the woman received approximately 16,000 dosage units of controlled substances with approximately 12,000 of those dosage units not legitimately prescribed or obtained.

A pharmacy technician with a major pharmacy chain was arrested after being videotaped placing tablets from two pharmacy bottles into her purse. The female was found to be in the possession of 100 tabs of hydrocodone and 99 tabs of clorazepate. She admitted to taking the drugs for personal use.

A man was sentenced for the illegal distribution of large quantities of Percocet, Vicodin (hydrocodone), Tylenol #3 and #4, Valium and Xanax.

A registered pharmacist was indicted on five charges of acquiring Lortab (7.5 mg, hydrocodone) by misrepresentation, fraud, forgery, or deception. The individual used the names of area physicians and their DEA registration numbers to forge scripts at the pharmacy where he was employed.

A registered pharmacist was arrested for obtaining Lortabs (7.5 mg, hydrocodone) by fraudulent means and for producing false documents. The individual was using personal computers in his apartment to create and duplicate controlled substance prescriptions.

The owners of a pharmacy settled a case involving the pharmacy filling approximately 43 forged prescriptions accounting for in excess of 16,000 tablets of Vicodin ES (7.5 mg, hydrocodone).

A male was arrested for diverting large quantities of drugs from a pharmacy and two pharmacy technicians confessed to diverting large quantities of a number of drugs, including 17,000 dosage units of hydrocodone.

A dentist was sentenced to five years probation and $750 fine and 160 hours of community service for unlawful prescribing of Lortab 7.5 mg (hydrocodone).

A dentist pled guilty to knowingly and intentionally acquiring possession of a controlled substance (Lortabs) by misrepresentation, fraud, forgery, deception, or subterfuge for his own personal use

A former male drug warehouse employee was arrested for theft and selling of multiple thousand dosage units of Vicodin (hydrocodone) in factory sealed bottles.

The Seattle Diversion Group seized all controlled substances on hand at a pharmacy. The pharmacist had not renewed his license. Accountability records at the pharmacy and at the hospital pharmacy where he had been previously employed revealed shortages of over 21,000 dosage units of Lortab and Lorcet.

A pharmacist was arrested and charged with one count of illegal possession of a controlled substance. The female pharmacist was diverting hydrocodone from her employer, Walmart Pharmacy.

New cases added on March 20, 2008

Following were some significant cases that were registered during the time frame of June 2004 through the present. Majority of these cases involve trafficking or seizures of at least 5,000 or more hydrocodone tablets. These cases were identified from G Scan database using search terms "seizures" "hydrocodone", "arrests" and "diversion". Some cases were retrieved from the STRIDE database using search criterion of cases involving a minimum of 5,000 hydrocodone tablets.

In early 2004, a Pharmacist was arrested and charged with illicit distribution of 14,300 hydrocodone combination tablets, 2,560 OxyContin® tablets, 6,000 Percocet tablets and 9,200 alprazolam tablets over a 20 month period.

In December 2004, DEA arrested an individual for illegally obtaining a controlled substance (hydrocodone) via prescription fraud. Over a several year period, the individual used his deceased Physician-father's prescription pad to write prescriptions for methylphenidate and hydrocodone. When arrested, he was in possession of 176 dosage units of hydrocodone.

In early 2004 investigators noted a pharmacy that was selling an inordinate amount of controlled substances, 80-90 percent of which were for hydrocodone combination products. In just 18 months, the pharmacy had ordered over 7.3 million dosage units of hydrocodone. Registration of the pharmacy was suspended.

In June 2004, nine individuals employed by a New Orleans Sheriff's office, including four Deputy Sheriffs, were arrested for trafficking in pharmaceutical controlled substances. The substances, which included hydrocodone, oxycodone, and Darvocet, were obtained by "doctor shopping." Once the controlled substances were obtained, they were sold for financial gain.

In June 2004, a six-month investigation culminated in the arrest of a medical doctor and two associates in Flint, MI, for prescribing controlled substances without a medical reason. During the period of January 2003 through April 2004, oxycodone and hydrocodone in combination with codeine cough syrup were illegally prescribed, which included 166,000 dosage units of hydrocodone.

In July 2004, an owner and operator of a pharmacy in Pittsburg, PA, pled guilty to illegally dispensing hydrocodone. The investigation revealed that the owner sold pharmaceutical controlled substances to individuals without a prescription over a four year period. Over 115,000 dosage units of schedules II to V controlled substances were seized.

In September 2004, a Pharmacist was indicted for diversion of prescription drugs. An accountability audit showed shortages of over 439,000 hydrocodone tablets.

In September 2004, two persons were arrested after giving consent to DEA agents to enter their residence at in Homerville, Georgia. In their possession were 8 Bottles of Hydrocodone/Bitartrate and Acetaminophen 7.5mg/ 500mg 500 count bottles, 7 bottles of Hydrocodone/Bitartrate and Acetaminophen 7.5mg/ 500mg 500 count bottles, 2 bottles of 10mg/325mg, 500 count bottles of Hydrocodone Bitartrate/Acetaminophen, and 1 vial of Testosterone Cyprionate Injection USP, 200mg/ml.

After a 19 month investigation, in December 2004, and after multiple undercover purchases, several individuals were arrested and charged with alleged distribution in excess of 1.4 million dosage units of generic hydrocodone products.

In December 2004, a federal search warrant was executed at a pharmacy located in Townsend, GA, to search the pharmacy's inventory records for methods of ordering and dispensing

controlled substances. This investigation was initiated based upon information that the owner and pharmacist were involved in the illegal distribution of controlled substances. Large quantities of hydrocodone syrup and other controlled substances were dispersed to numerous subjects without the use of a prescription. An accountability audit revealed a shortage of 436,733 dosage units of hydrocodone for a period of one year and eight months.

In February 2005, a Pharmacist was arrested and charged with illegal distribution of methadone, oxycodone, hydrocodone, Xanax and Talwin which he allegedly diverted without legitimate medical purpose, largely in exchange for sexual favors.

In 2005 there have been 48 night break-in burglaries in retail pharmacies in Washington State. The primary drugs taken were oxycodone, hydrocodone, morphine, Ritalin, fentanyl and methadone. The break-in are believed to been carried out by a single drug trafficking organization.

In April 2005, surveillance of a suspected diversion of a controlled substance (pills) from pharmacy in Jersey City, NJ resulted in two arrests and the seizure of 119,000 hydrocodone tablets. The seizure and arrests were made while surveillance followed the suspects transporting the pills from the pharmacy to an undisclosed location.

An Organized Crime Drug Enforcement Task Force investigation resulted in the closing of a 'script mill' in April 2005 and arrest of three Doctors and immediate suspension of the registration of four pharmacies for conspiracy to illegally distribute hydrocodone, alprazolam and carisoprodol. In operation since 1998, the clinics and pharmacies operated on a cash only basis and the doctors saw between 100-300 patients and wrote more than 200 prescriptions daily.

In April 2005, DEA conducted an arrest and seizure in Sierra Blanca, TX of a total of sixteen (16) one-pint bottles of Tussionex Hydrocodone Polisterex and assorted pills. The pills totaled 2,998 Maxidone Hydrocodone pills, 3,694 OxyContin® 80mg pills, 115 OxyContin® 40mg pills, 3,997 Dilaudid hydromorphone 4mg pills, and 1,000 alprazolam 2mg pills.

During May 2005, DEA made undercover purchases of 1,500 hydrocodone tablets from a Physician without legitimate medical reason. Subsequent arrest of the Physician ensued and pursuant to a search warrant $1.35 million in bulk currency recovered from his home.

In May 2005, an employee of hospital was arrested and confessed to stealing hydrocodone from the hospital pharmacy on a weekly basis. Suspected quantities of hydrocodone included three to six 500 count bottles of hydrocodone per week.

[redacted]

In November 2005, law enforcement officials initiated the execution of a state search warrant in Eden Prairie, MN. This resulted in the arrest of a suspect and the seizure of 12,366 tablets of hydrocodone. The suspect stated that he uses some of the pills for pain, and sells the remaining. The suspect trades cocaine for the hydrocodone, which is obtained from a person who works in a local pharmacy.

[redacted]

In November 2005, guilty pleas to conspiracy to distribute hydrocodone bitartrate and alprazolam were made in the Western District of Louisiana. This investigation was initiated as a result of a traffic stop whereby 9,000 D.U. of Hydrocodone, 9,500 D.U. of alprazolam and 22 pounds of marijuana were located and seized. The controlled substances were destined for Eunice, Louisiana.

[redacted]

Following multiple undercover purchases a Physician was arrested for illicit distribution of hydrocodone, oxycodone and phendimetrazine. During December 2005, the Physician purchased over 40,000 dosage units of hydrocodone.

[redacted]

In May 2006, an individual was arrested following the undercover purchase of 2,000 Vicodin, 10,000 Valium and 700 OxyContin® tablets.

[redacted]

In June 2006, following undercover purchases of 2,500 hydrocodone tablets and additional purchases of 4,000 tablets, DEA arrested two individuals. One individual was employed as a pharmacy technician.

[redacted]

In May 2006, a State of California search warrant was executed at the residence in San Diego, CA that resulted in an arrest. An undetermined amount of suspected cocaine, various tablets of suspected Diazepam, and miscellaneous drug paraphernalia were seized. DEA reports 13,396 tablets of hydrocodone associated with this case.

[redacted]

In October 2006, a Federal search and seizure warrant was executed on a health care facility in Baltimore, MD. Among the documents seized were numerous boxes containing copies of internet prescriptions filled by the health care facility. Seized were 2,174 prescriptions for combination hydrocodone products, which totaled 192,480 dosage units. DEA STRIDE system reported 351,508 tablets of hydrocodone seized.

[redacted]

DEA reported the arrest of a Physician in 2006 based upon belief that he was profiting $50,000 per month in dispensing prescriptions for pain medications including hydrocodone (primarily Lorcet and Vicodin ES).

[redacted]

After the arrest of a Physician by DEA in November 2006, patients began visiting another Physician for diversion of hydrocodone via illicit prescriptions. Undercover purchases were made by DEA and an arrest warrant was issued for the second Physician for illicit distribution of hydrocodone.

[redacted]

In April 2007, a federal search warrant was executed at a residence in Tyler, Texas. Several thousand tablets of hydrocodone and alprazolam were seized. Multiple 500 count bottles of hydrocodone were kept at the residence. The suspect has talked of purchasing 5,000 tablets at a time from a source in Houston, Texas.

[redacted]

In April 2007, a search warrant on a residence located in Portland, Oregon was executed. An employee of Walgreens diverted pharmaceutical controlled substances 1-2 times per week, diverting approximately 200 to 700 dosage units per transaction. In total, there were estimated 75 - 100 transactions. The search revealed tablets contained in Walgreens bottles, which were diverted through forged prescriptions. DEA's STRIDE system reports 20,447 tablets of hydrocodone associated with this case.

[redacted]

In May 2007, subsequent to a traffic stop, a person was arrested in possession of approximately twenty six pounds of hydrocodone tablets. The suspect stated that the hydrocodone was obtained in Grand Prairie, Texas and was being transported to Jackson, Mississippi.

[redacted]

In June of 2007 a hydrocodone distributor agreed to pay $800,000 in fines pursuant to a consent judgment for distribution of over 9 million dosage units of hydrocodone to 18 rogue internet pharmacies for filling of prescriptions in absence of Doctor-Patient relationship.

[redacted]

In December 2007, a full confession was obtained from the controlled substances buyer for a pharmacy in Tulsa, AZ. The buyer diverted approximately 399,500 dosage units of hydrocodone and 234,000 dosage units of alprazolam from July 2006 through June 2007.

[redacted]

In June 2007, a person admitted perpetrating the theft of a commercial tractor-trailer transporting over 16.6 million tablets of hydrocodone from a truck stop in Troy, Illinois. A total of 16,660,400 dosage units of hydrocodone combination products were stolen. The tractor and trailer were recovered separately, with the cargo found almost intact.

[redacted]

In August 2007, DEA Diversion Investigators traveled to Chicago, Illinois, to speak with a DEA registrant (MD) in regards to excessive ordering of hydrocodone (Vicodin) in various strengths. In an eighteen month period (January 2006 – June 2007) the registrant ordered 3,498,276 dosage units of hydrocodone product. Prescriptions were filled after receiving a patient's chart, which

was obtained via the internet. The doctor surrendered his DEA Registration Certificate for violating the Controlled Substance Act.

In September 2007, a federal search warrant was executed on a car registered to a Medical Doctor. Agents began surveillance of this person's home in Jackson, TN. Among the items seized in this investigation were 6,139 tablets of hydrocodone and 3,388 tablets of alprazolam. A federal grand jury returned a three count indictment against the suspect for possession of hydrocodone and alprazolam and conspiracy to distribute hydrocodone.

In May 2007, a Michigan Doctor was indicted for illegal distribution of controlled substances. From January 2003 to May 2006 he wrote prescriptions for over 670,000 dosage units of hydrocodone for no known medical reason.

In June 2007, DEA arrested two individuals as they attempted to sell 8,000 OxyContin® 80mg tablets to a cooperating defendant. After the arrest, 4,000 hydrocodone tablets were found in their vehicle.

Beginning March 2006, DEA received information regarding the illicit prescribing of hydrocodone without any exam, testing or medical necessity. During surveillance, the Physician was observed meeting patients in the parking lot of the clinic and issuing prescriptions. Patients would then drive directly to Pharmacy to fill hydrocodone prescriptions. DEA made several undercover purchases and an arrest warrant issued. The Physician was documented as sending approximately $30,000 per month to an overseas account.

The owner of a pharmacy was arrested after several months long investigation in which he was observed selling controlled substances without valid prescription in exchange for cash, sex and liquor. An audit showed a shortage of 464,456 units of Lortab and 124,682 units of hydrocodone.

In December 2007, a Houston based Pharmacist was charged as financier and leader of an interstate trafficking group which distributed large quantities of hydrocodone and recruited individuals to hire homeless people who were paid to obtain prescriptions from a Physician co-conspirator. Revenues approached $18 million per year. On three separate occasions between November and December 2006 undercover agents purchased total of 8,000 dosage units of hydrocodone.

In September 2007, culminating a year long investigation, DOJ issued an indictment for a pharmacy that included a money judgment of $20 million based on the illegal distribution of 9 million dosage units of hydrocodone.

[redacted]

In January 2008, a 54 count indictment against the Physician Operator of a pain clinic was issued for prescribing millions of dosage units of hydrocodone products to individuals without legitimate medical use. The Physician charged $500 cash per person for first visit and $300 for follow-up visits to receive a prescription without medical exam, to be dispensed from one of three different pharmacies.

[redacted]

In February 2008, DEA executed search warrants on two pain management clinics specializing in treatment of chronic pain. These clinics were operating as "pill mills" and DEA made undercover purchases of hydrocodone and OxyContin® prescriptions. The unlawful prescribing from these clinics has resulted in at least seven documented deaths in the Pensacola area.

[redacted]

In March 2008, three pharmacies in San Diego, CA, all owned by a single pharmacist, were involved in the diversion of large amounts of hydrocodone (including Vicodin) and oxycodone. In one pharmacy, over 90,000 hydrocodone tablets were distributed illegally and in another, 5,449 hydrocodone tablets were diverted in a single month. DEA's STRIDE system reports that 13,396 hydrocodone tablets were seized in this investigation.

[redacted]

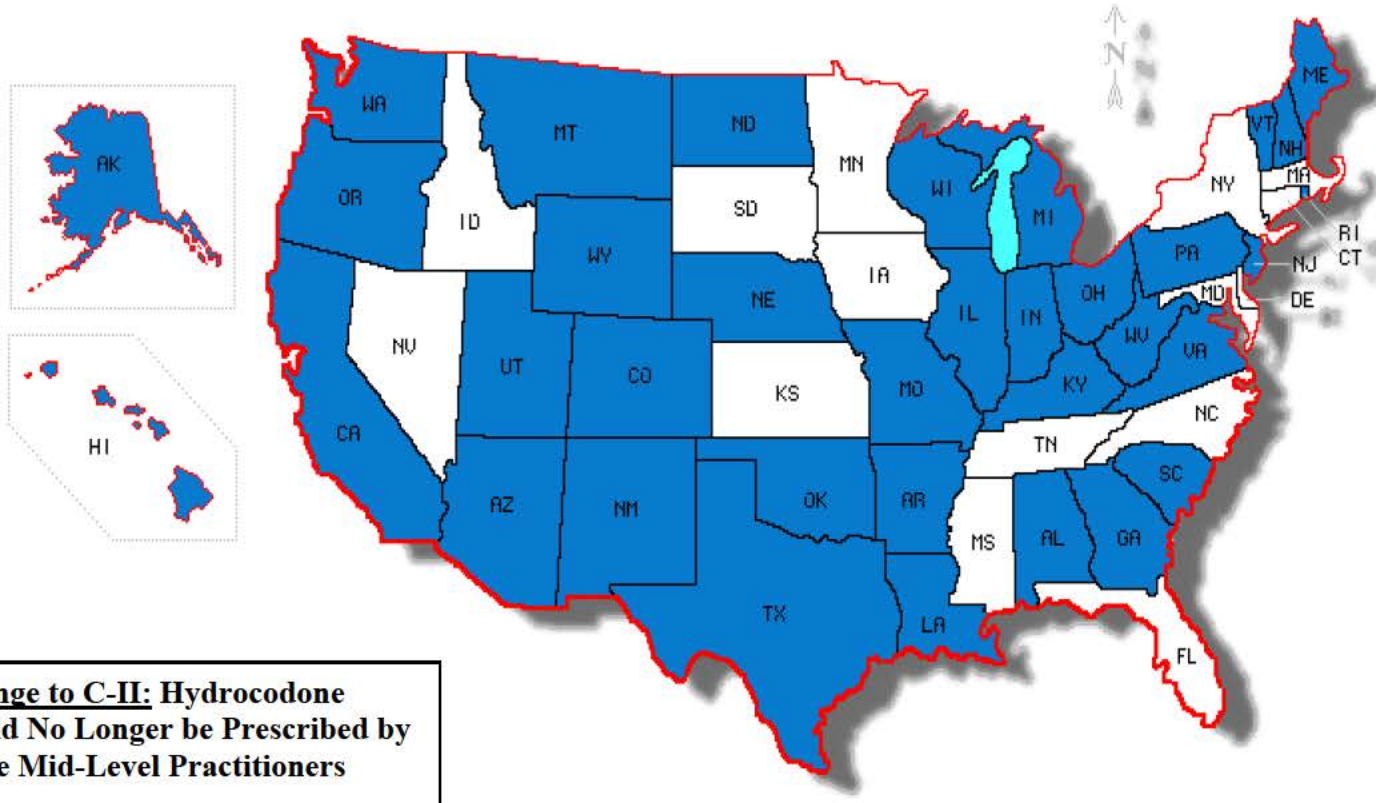
In March 2008, a civil pre-complaint offer was signed with the owner of a pharmacy and medical supply located in Houston, TX. The pharmacy was purchasing excessive amounts of controlled substances in schedule III and IV, including hydrocodone products, and filled prescriptions without identification. A March 2007 audit revealed shortages of 47,081 dosage units for hydrocodone, APAP with codeine and alprazolam.

Controlled Substance Act- Schedules and Regulatory Requirements

	Schedule I	Schedule II	Schedule III	Schedule IV	Schedule V
Registration	Required	Required	Required	Required	Required
Recordkeeping	Separate	Separate	Readily retrievable	Readily retrievable	Readily retrievable
Distribution Restrictions	Order forms	Order forms	Records required	Records required	Records required
Dispensing Limits	Research use only	Rx: written no refills	Rx: written or oral; refills Note 1	Rx: written or oral; refills Note 1	OTC (Rx drugs limited to MD's order
Manufacturing Security	Vault/safe	Vault/safe	Secure storage area	Secure storage area	Secure storage area
Manufacturing Quotas	Yes	Yes	NO but some drugs limited by Schedule II	NO but some drugs limited by Schedule II	NO but some drugs limited by Schedule II
Import/Export Narcotic	Permit	Permit	Permit	Permit	Permit to import; declaration to export
Import/Export Non-Narcotic	Permit	Permit	Note 2	Declaration	Declaration
Reports to DEA by Manufacturer/Distributor Narcotic	Yes	Yes	Yes	Manufacturer only	Manufacturer only
Reports to DEA by Manufacturer/Distributor Non-Narcotic	Yes	Yes	Note 3	Note 3	No

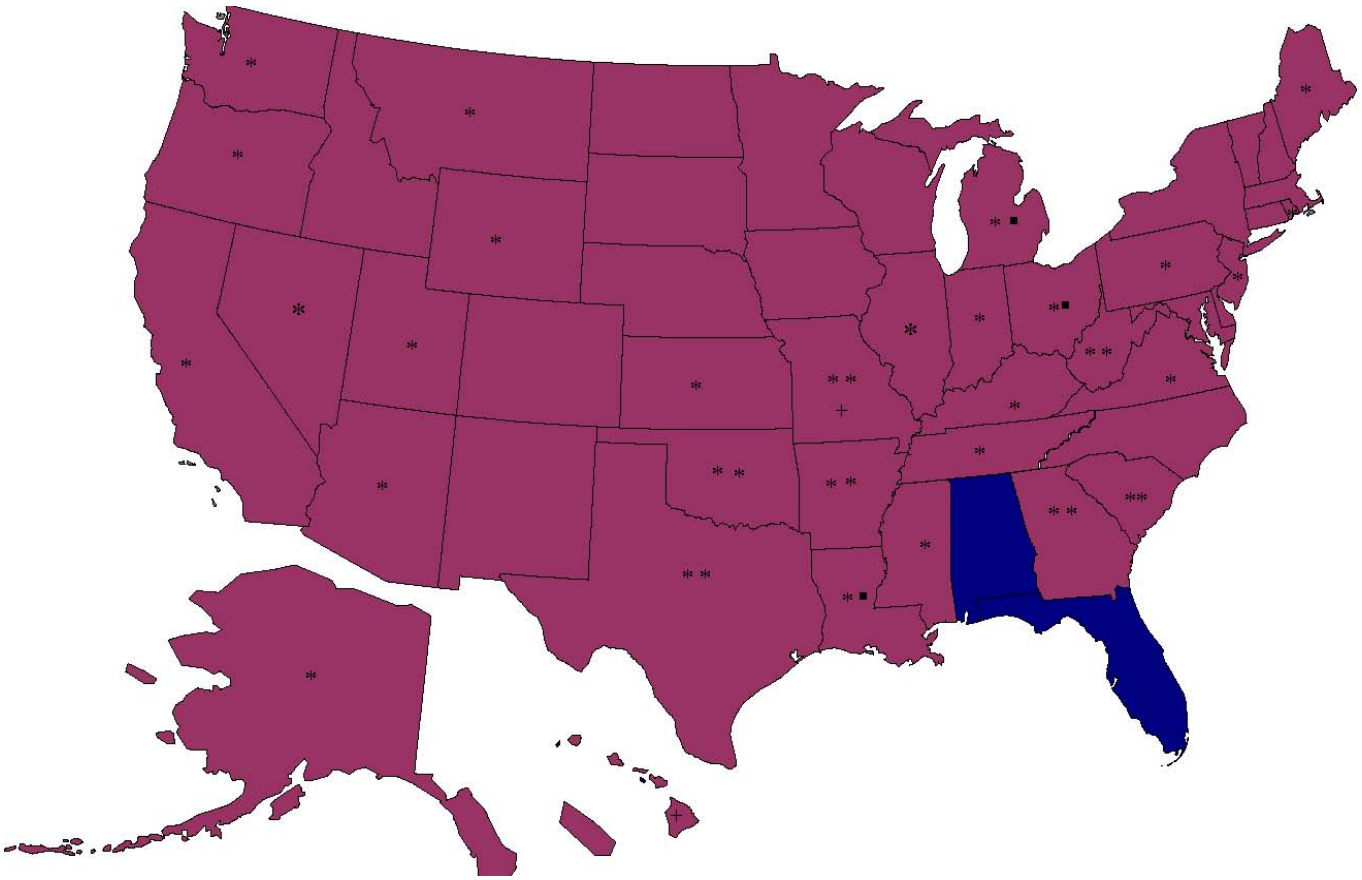
Accessed at http://druglibrary.net/schaffer/dea/pubs/abuse/chap1/penal/chart3.htm on April 13, 2012.

Prescribing Authority by States for Physician Assistants, Nurse Practitioners, and Optometrists



<u>Change to C-II:</u> Hydrocodone Could No Longer be Prescribed by Some Mid-Level Practitioners

<u>Most affected</u>: Optometrists (30)
<u>Next affected</u>: Physician Assistants (14) and Nurse Practitioners (13) (Some states are CII restrictions only)
<u>Ref:</u> Mid-Level Practictioners Authorization by State. DEA. Link: http://www.deadiversion.usdoj.gov/drugreg/practioners/mlp_by_state.pdf . Accessed 1/18/2012



NURSE PRACTITIONER PRESCRIPTIVE AUTHORITY

States That Prescribe Legend Drugs Only States Recognized by DEA with Authority to

Prescribe Controlled Substances

* Schedule II-V Only

* * Schedule III-V Only

* * * Schedule V Only Schedule

■ Schedule II restrictions

+ Pending DEA Approval

There are 2 states in which NPs do not have privilege to prescribe controlled substances. These states (AL and FL are seen in blue in the map above)

Assessed at http://www.aanp.org/ on May 1, 2012.

PA Prescribing Authority by State

Jurisdiction	Restrictions	Controlled Substances
Alabama		Sch. III-V
Alaska		Sch. II-V
Arizona		Sch. II-III limited to 30-day supply with board prescribing certification (72-hrs. without), no refills without written consent from supervising physician; Sch.IV-V not more than 5 times in 6-month period per patient
Arkansas		Sch. III-V
California		Sch. II-V[1]
Colorado		Sch. II-V
Connecticut		Sch. II-V
Delaware		Sch. II-V
District of Columbia		Sch. II-V
Florida	Formulary of prohibited drugs	
Georgia	Formulary	Sch. III-V
Guam		Sch. III-V
Hawaii		Sch. III-V
Idaho		Sch. II-V
Illinois		Sch. II-V
Indiana		Sch. III-V (limited 30-day supply)
Iowa		Sch. II-V; Sch. II (except depressants)
Kansas		Sch. II-V
Kentucky		
Louisiana		Sch. III-V
Maine		Sch. III-V (Medical Board may approve Sch. II for individual PAs practicing with MD supervision. No such provision for Osteopathic board.)
Maryland		Schedule II-V
Massachusetts		Schedule II-V
Michigan		Sch. II-V
Minnesota	Formulary	Sch. II-V
Mississippi		Sch. II-V
Missouri		Sch. III-V (Sch. III limited to 5-day supply with no refill)

AAPA Advocacy and Government Relations

Assessed at http://www.aapa.org on April 17, 2012

PA Prescribing Authority by State

Jurisdiction	Restrictions	Controlled Substances
Montana		Sch. II-V (Sch. II limited to 34-day supply)
Nebraska		Sch. II-V
Nevada		Sch. II-V
New Hampshire		Sch. II-V
New Jersey		Sch. II-V (certain conditions apply)
New Mexico	Formulary	Sch. II-V
New York		Sch. II-V
North Carolina		Sch. II-V (Sch. II-III limited to 30-day supply)
North Dakota		Sch. II-V
Ohio	Formulary	Sch. III-V
Oklahoma	Formulary	Sch. III-V (limited to 30-day supply)
Oregon		Sch. II-V
Pennsylvania		Sch. II-V (Sch. II limited to 72 hours for initial therapy; 30 days for ongoing therapy)
Rhode Island		Sch. II-V
South Carolina		Sch. III-V
South Dakota		Sch. II-V (Sch. II limited to 30-day supply)
Tennessee		Sch. II-V
Texas		Sch. III-V (limited to 30-day supply)
Utah		Sch. II-V
Vermont		Sch. II-V
Virginia		Sch. II-V
Washington		Sch. II-V
West Virginia	Formulary	Sch. III-V (Sch. III limited to 72-hour supply)
Wisconsin		Sch. II-V
Wyoming		Sch. II-V

STATES PERMITTING OPTOMETRISTS TO PRESCRIBE CONTROLLED (Narcotic) LEGEND DRUGS					
STATE	**Schedule I**	**Schedule II**	**Schedule III**	**Schedule IV**	**Schedule V**
ALASKA[17]			X	X	X
ALABAMA[7]			X	X	X
ARIZONA			X		
ARKANSAS			X	X	X
CALIFORNIA[10][11]			X		
COLORADO			X	X	X
CONNECTICUT		X	X	X	X
GEORGIA[5]			X	X	
IDAHO		X	X	X	X
ILLINOIS[16]			X	X	X
IOWA		X	X	X	X
KANSAS		X	X	X	X
KENTUCKY[8]			X	X	X
LOUISIANA[15]			X	X	X
MAINE[18]			X	X	X
MICHIGAN[13]			X	X	X
MINNESOTA				X	
MISSISSIPPI				X	X
MISSOURI		X	X	X	X
MONTANA[2]		X	X	X	
NEBRASKA[2][6]		X	X	X	X
NEVADA[8]		X	X	X	X
NEW HAMPSHIRE[3]			X	X	
NEW JERSEY			X	X	X
NEW MEXICO[2]			X	X	X
NORTH CAROLINA		X	X	X	X
NORTH DAKOTA[9]			X		
OHIO			X		
OKLAHOMA			X	X	X
OREGON[12]			X	X	X
PENNSYLVANIA			X	X	X
RHODE ISLAND			X	X	X
SOUTH CAROLINA			X	X	X
SOUTH DAKOTA[2]		X	X	X	X
TENNESSEE[4]		X	X	X	X
TEXAS[6][10]		X	X	X	X
UTAH[8]			X	X	X
VERMONT			X	X	X
VIRGINIA[2][8]			X	X	
WASHINGTON[14]			X	X	X
WEST VIRGINIA[10]			X	X	X
WISCONSIN[2]			X	X	X
WYOMING			X	X	X

Last Revised April 26, 2012

FOOTNOTES:

1. Reserved.
2. Treatment for ocular pain and inflammation.
3. Treatment with only those oral analgesic drugs included in the formulary.
4. Therapeutically-certified ODs may utilize any pharmaceutical agent rational to the treatment of eye disease.
5. Treatment with controlled analgesic drugs over 72 hours may not be done without consultation with the patient's physician.
6. Within the Schedule II category - topical only is permitted (this would be the one controlled drug available for diagnostic purposes)
7. Within the Schedule III category - no agents containing dihydrocodeinone ("hydrocodone"), other Schedule III drugs limited to Rx not to exceed 96 hours.
8. Prescriptions limited to dosages for no more than 72 hours.
9. Treatment with acetaminophen plus 30mg of codeine only.
10. Prescription of analgesics for a duration of no more than 3 days.
11. Compounds containing codeine or hydrocodone only.
12. Treatment with Schedule III analgesics longer than 7 days requires consultation with an MD.
13. Plus may prescribe dihydrocodeinone combination drugs, no matter what class they are scheduled in.
14. Prescription for controlled narcotic substance may not be for more than 7 days for a single condition, trauma, episode.
15. Rx of narcotic for 48 hours only. May be followed with one additional 48 hour Rx if warranted by follow-up exam.
16. Prescriptions limited to analgesics in dosages for no more than 72 hours.
17. Prescriptions limited to 4 days quantity.
18. Prescriptions limited to one 5 day supply of analgesics in Schedules III, IV, and V.

State optometry acts specifically prohibiting optometrists from prescribing controlled (narcotic) legend drugs: Delaware, Hawaii, Indiana, and Massachusetts (when referring to this list of states which specifically prohibit the prescription of controlled drugs, remember that other states not listed here authorizing "topical agents only" or "specific categories only" could essentially prohibit the use of controlled narcotic drugs as well.)

Accessed at www.deadiversion.usdoj.gov on April 26, 2012

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