Schedules of Controlled Substances:

Placement of Hydrocodone Combination Products into Schedule II

Background, Data, and Analysis:

Eight Factors Determinative of Control

and

Findings Pursuant to 21 U.S.C. 812(b)

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I. Introduction

In January 1999, the Drug Enforcement Administration (DEA) received a petition from a practicing physician specialized in addiction medicine requesting that proceedings be initiated to reschedule hydrocodone combination products 1 (HCPs) from schedule III to schedule II of the Controlled Substances Act (CSA). The petition contends that evidence of abuse potential is sufficient for HCPs 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)), the DEA gathered the necessary data and on July 28, 2004, forwarded that information to the Department and Health and Human Services (HHS) for a scientific and medical evaluation and scheduling recommendation. On March 6, 2008, the Assistant Secretary for Health, HHS, forwarded to the Deputy Administrator of DEA a scientific and medical evaluation 2 entitled, “Basis for the Recommendation to Maintain Hydrocodone Combination Products in schedule III of the Controlled Substances Act” and a letter recommending that HCPs continue to be subject to control under schedule III of the CSA. The HHS scientific and medical evaluation 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 for Health in preparing the above review with respect to HCPs 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 the DEA, as delegated by the Attorney General 3 to determine whether the HHS 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. 21 U.S.C. 811(b). Because “other relevant data” contained substantial amount of new information, on February 13, 2009, the DEA, in accordance with the CSA (21 U.S.C. 811(b)), submitted the same to HHS and requested to reevaluate this petition and provide a scheduling recommendation.

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1 Hydrocodone combination products (HCPs) are pharmaceuticals containing specified doses of hydrocodone in combination with other drugs in specified amounts. These products are approved for marketing for the treatment of pain and for cough suppression.
2 As set forth in a memorandum of understanding entered into by the HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary’s scheduling responsibilities under the CSA, with the concurrence of the NIDA. 50 FR 9518, Mar. 8, 1985. The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations.
3 28 CFR 0.100(b)
The HHS, on December 16, 2013, forwarded to the Administrator of DEA its scientific and medical evaluation (henceforth called HHS review) entitled, “Basis for the Recommendation to Place Hydrocodone Combination Products in Schedule II of the Controlled Substances Act” and a letter recommending that HCPs be controlled in schedule II of the CSA.

The CSA requires the DEA, as delegated by the Attorney General, to determine whether HHS’s scientific and medical evaluation and all other relevant data constitute substantial evidence of potential for abuse such that the substance should be rescheduled as proposed in the petition. 21 U.S.C. 811(b). This document is a review of these data and a determination to place HCPs into Schedule II of the CSA.

II. Background: HCPs

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 as the following (21 CFR §1308.13 (e)):

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

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 of the CSA.

HHS’s review on HCPs states that these products are approved for marketing for the treatment of pain and for suppression of cough. Hydrocodone in combination with other analgesics has an important and legitimate role for the treatment of pain. These products include hydrocodone combined with nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. Hydrocodone in combination with anti-tussives or antihistamines, has an important and legitimate role for the symptomatic relief of cough and upper respiratory symptoms associated with cold and allergy in adults and in children six years of age and older.

HHS review suggested the following potential clinical rationale for the less restrictive

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4 28 CFR 0.100(b)
5 In the United States there are currently no approved, marketed, products containing hydrocodone in combination with other active ingredients that fall outside schedule III of the CSA. Further, until recently, there were no approved hydrocodone single-entity schedule II products. In Oct. 2013, the FDA approved Zohydro ™ ER, a single-entity, extended release schedule II hydrocodone product. The sponsor of this product in a press release dated Oct. 25, 2013 stated that Zohydro ™ ER will be launched in approximately four months. Accordingly, all of the historical data regarding hydrocodone from different national and regional databases that support this proposal should refer to HCPs only, regardless of whether the database utilizes the term “hydrocodone” or “hydrocodone combination products.”
schedule for HCPs compared to the schedule for hydrocodone substance. The potentiation of therapeutic effect (analgesia) of hydrocodone by the nonnarcotic active ingredient present in HCPs reduces the amount of hydrocodone needed to achieve the desired therapeutic effect thereby reducing adverse events. As a consequence, a proportionate reduction in the other pharmacological effects (including euphoria and drug liking) of hydrocodone present in these combination products is likely to occur and thus reducing the potential for abuse. DEA notes that although this is a favorable scenario for a patient who is not a drug abuser, it is unlikely to be a deterrent for typical drug abusers from abusing these drug formulations as this scenario can be overcome by increasing the number of unit doses ingested. Further, some HCPs contain nonnarcotic substance that is not analgesic (e.g. Hycodan® containing homatropine). Thus the above rationale based on analgesia potentiation does not apply to all HCPs.

The HHS states that HCPs are widely prescribed in the United States (U.S.). The HHS mentioned that 131 million prescriptions for hydrocodone-containing combination analgesic products were dispensed to over 47 million patients in 2011. The corresponding numbers for oxycodone-containing products (schedule II) were 34.6 million prescriptions for approximately 15.1 million patients. In 2011, approximately 5 million prescriptions for hydrocodone-containing combination antitussive products were dispensed. The total number of hydrocodone-containing tablets dispensed in the U.S. in 2012 was approximately 8 billion tablets and about 74% of these tablets were dispensed towards “new prescription.” Primary care practitioners prescribed about half of the total tablets containing hydrocodone, while pain specialists and dentists prescribed a small percentage of the total tablets. Primary care practitioners prescribed a median of 60 tablets per each prescription as compared to 20 tablets by emergency physicians and 40 tablets by other specialties.

III. Eight Factors Determinative of Control

Pursuant to 21 U.S.C. 811(c), DEA must consider eight factors in making any finding of substantial evidence of potential for abuse, including the data and law enforcement information relevant thereto.

1. ITS ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

The term “abuse” is not defined in the CSA. However, the legislative history of the CSA suggests the following criteria in determining whether a particular drug or substance has a potential for abuse:

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

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6 The term “new prescription” refers to an initial prescription, either paper or telephoned as opposed to a refill.
7 Primary care practitioners include general practice, internal medicine, family medicine, and Doctor of Osteopathy.
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.**

The HHS states that multiple factors must be considered in determining the abuse potential of any substance. 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 and relationship to a substance already listed. Animal data and epidemiological data are both used in determining a substance’s abuse liability. A comprehensive evaluation of abuse potential of a drug substance includes consideration of its receptor binding and functional properties, preclinical pharmacology, discriminative stimulus effects, reinforcing effects, dependence potential, pharmacokinetics, routes of administration, clinical abuse potential studies, assessment of efficacy-safety relative to actual abuse, toxicities, and the public health risks. Epidemiological data also is 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.

The DEA considered the HHS’s evaluation and all other relevant data, including data related to the above mentioned criteria, and finds that:

a. **Individuals are taking HCPs 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)\(^9\) data indicate that abuse of HCPs has been associated with large number of admissions to the emergency department (ED). For

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\(^9\) The DAWN is a nationally representative public health surveillance system that continuously monitors drug-related visits to hospital EDs. The DAWN data are used to monitor trends in drug misuse and abuse in the United States. DAWN gathers data on drug abuse-related ED visits from a representative sample of hospitals in the coterminous United States. To be eligible for selection into the DAWN sample, a hospital must be a non-federal, short-stay, general surgical and medical hospital located in the United States, with at least one 24-hour ED. A DAWN case is any ED visit involving recent drug use that is implicated in the ED visit. DAWN captures both ED visits that are directly caused by drugs and those in which drugs are a contributing factor but not the direct cause of the ED visit. Annually, DAWN produces estimates of drug-related visits to hospital EDs for the nation as a whole and for selected metropolitan areas. In DAWN, nonmedical use of pharmaceuticals includes taking more than the prescribed dose of a prescription pharmaceutical or more than the recommended dose of an over-the-counter pharmaceutical or supplement; taking a pharmaceutical prescribed for another individual; deliberate poisoning with a pharmaceutical by another person; and documented misuse or abuse of a prescription drug, an over-the-counter pharmaceutical, or a dietary supplement. Nonmedical use of pharmaceuticals may involve pharmaceuticals alone or pharmaceuticals in combination with illicit drugs or alcohol. DAWN also captures limited data on drug-related
example, in 2011 the total numbers of ED visits related to nonmedical use of HCPs and oxycodone products\textsuperscript{10} were 82,480 and 151,218, respectively.

- DAWN medical examiner (ME) data for five states indicate that from 2004 through 2010, deaths related to HCPs and oxycodone products increased by 63% and 133%, respectively.
- According to the American Association of Poison Control Centers’ National Poison Data System\textsuperscript{11} (NPDS; formerly known as Toxic Exposure Surveillance System or TESS), HCPs were involved in 30,792 and 29,391 annual toxic exposures in 2011 and 2012, respectively. The corresponding numbers for oxycodone products were 19,423 and 18,495.
  - Majority of exposures for both drug products were for intentional reason\textsuperscript{12}.
  - Annual rates of abuse and misuse (calculated as intentional toxic exposures expressed as percent of all types of toxic exposures) of HCPs are slightly higher than the corresponding rates for oxycodone products.
- According to the Florida Department of Law Enforcement (FDLE)\textsuperscript{13}, HCPs have been associated with large number of deaths in Florida in recent years. For example, in 2012, HCPs were associated with 777 deaths, while oxycodone products were associated with 1,426.

\textit{b. There is significant diversion of HCPs from legitimate drug channels.}

- According to the forensic laboratory data as reported by the National Forensic Laboratory System\textsuperscript{14,15} (NFLIS) and the System to Retrieve Information from Drug Evidence\textsuperscript{16}...
(STRIDE), HCPs, similar to oxycodone products, are among the top 10 most frequently encountered drugs. From 2002 through 2010, total cases for both HCPs and oxycodone products gradually increased with some decline in 2011 and 2012. From 2002 through 2008, annual total cases involving HCPs (range: 9,106 in 2002 to 33,611 in 2008) consistently exceeded those for oxycodone products (range: 7,993 in 2002 to 28,343 in 2008). In 2009, total cases for HCPs (37,894) were similar to that for oxycodone products (37,680). From 2010 through 2012, total cases for oxycodone products (47,238 in 2010 and 41,915 in 2012) exceeded those for HCPs (39,261 in 2010 and 34,832 in 2012).

- The DEA has documented a large number of diversion and trafficking cases involving HCPs.
- DEA investigations conducted from 2005 through 2007 found that HCPs were 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 kilograms (as base form of the drug) of HCPs from 2005 through 2007.
  - Average amounts of HCPs 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 HCPs ordered.

- Individuals are using HCPs on their own initiative rather than on the basis of medical advice.
- The HHS reviewed the data from the National Survey on Drug Use and Health (NSDUH) and found that the lifetime (i.e., ever used) users of HCPs for nonmedical

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15 While NFLIS data are not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. 76 FR 77330, 77332, Dec. 12, 2011

16 The STRIDE, a DEA database, reports the results of drug evidence analyzed at DEA laboratories nationwide. These drug exhibits (or items) are submitted to the laboratory as drug evidence from seizures and undercover purchases.

17 The National Survey on Drug Use and Health, formerly known as the National Household Survey on Drug Abuse (NHSDA), is conducted annually by the Department of Health and Human Service’s Substance Abuse and Mental Health Services Administration (SAMHSA). It is the primary source of estimates of the prevalence and incidence of nonmedical use of pharmaceutical drugs, illicit drugs, alcohol, and tobacco use in the United States. The survey is based on a nationally representative sample of the civilian, non-institutionalized population 12 years of age and older. The survey excludes homeless people who do not use shelters, active military personnel, and residents of institutional group quarters such as jails and hospitals. The NSDUH provides yearly national and state level
purpose exceeded those for oxycodone products in the U.S. For example, in 2004, over 17.7 million Americans age 12 years or older reported lifetime nonmedical use of HCPs as compared to over 11.9 million reported for oxycodone products. In 2012, the corresponding numbers for HCPs and oxycodone products were over 25.6 and 16 million, respectively. The NSDUH also reported large increases from 2004 through 2012 in the number of individuals using HCPs and oxycodone products for nonmedical purposes.

- The past year initiates (i.e., the first use of a substance within the 12 months prior to the interview date) of HCPs exceeded those of oxycodone products from 2002 through 2005. Past year initiates for HCPs were over 1.3, 1.4, 1.3 and 1.3 million in 2002, 2003, 2004 and 2005, respectively. The corresponding numbers for oxycodone products were over 0.47, 0.5, 0.6 and 0.45 million.
- According to a report by the NSDUH, the combined data from 2002 through 2005 indicate that 57.7% of persons who first used pain relievers nonmedically in the past year used HCPs while 21.7% used oxycodone products.
- The NSDUH data from 2002 through 2006 also indicate that the lifetime users of HCPs have higher propensity than that of lifetime users of oxycodone immediate release products (single-entity and combination products combined) to have used for nonmedical purpose any pain relievers in the past year.
- According to the Monitoring the Future (MTF) survey, from 2002 through 2011 the annual prevalence of nonmedical use of Vicodin®, a HCP, ranged from about 8 to 10.5% among high school seniors (12th graders) and exceeded that of OxyContin® (4 to 5.5%), an oxycodone extended release product. In 2012, the annual prevalence rates for nonmedical use of OxyContin® were 1.6%, 3.0%, and 4.3% among 8th, 10th and 12th graders. The corresponding rates for Vicodin® were 1.3%, 4.4% and 7.5%.
- According to the MTF survey, the annual prevalence of nonmedical use of Vicodin® in college students and young adults were 3.8% and 6.3%, respectively. The corresponding numbers for OxyContin® were 1.2% and 2.3% in 2012 (Johnston et al., 2012).

\( d. \) HCPs are 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 (schedule II) possesses abuse liability effects substantially similar to morphine (schedule II) in both animals and humans. Hydrocodone, similar to morphine, is a \( \mu \) opioid receptor agonist and shares pharmacological properties with morphine. Hydrocodone substitutes for morphine in animals trained to discriminate the presence and absence of morphine. Hydrocodone, similar to morphine, is self-administered by animals. Hydrocodone substitutes for morphine in opioid-dependent human subjects.
- Hydrocodone/acetaminophen and oxycodone/acetaminophen combination products at equi-miotic doses, in general, produce similar profile of psychopharmacological effects. These two opioid products produced prototypic opiate-like effects and psychomotor

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estimates of drug abuse, and includes prevalence estimates by lifetime (i.e., ever used), past year and past month abuse or dependence.

18Monitoring the Future (MTF) is a national survey conducted by the Institute for Social Research at the University of Michigan under a grant from the National Institute on Drug Abuse (NIDA) that tracks drug use trends among American students in the 8th, 10th, and 12th grades.
impairment of similar magnitudes. Acetaminophen, the nonnarcotic analgesic ingredient present in majority of the currently marketed HCPs, at clinically relevant doses lacks psychoactive effects.

- Clinical abuse liability studies have also demonstrated that HCPs (Hycodan® or hydrocodone in combination with acetaminophen) are similar to morphine with respect to physiological effects, subjective effects, and drug “liking” scores.

Collectively these data demonstrate that HCPs have a high potential for abuse similar to other schedule II opioid analgesic drugs such as morphine and oxycodone products. The following sections describe the data DEA considered in making this finding.

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 and is an agonist at these receptors (Gutstein and Akil, 2006). Similar to other morphine-like drugs, hydrocodone produces analgesia, suppression of cough reflex, respiratory depression, miosis and reduction in gastrointestinal motility and has the potential of being abused.

1.1.1. Abuse liability: Preclinical studies

All preclinical screening for abuse liability has involved the hydrocodone and not HCPs.

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 (Schuster and Johanson, 1988; Kamien et al., 1993; Balster and Prescott, 1992; Dykstra et al., 1997). 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 reference drug of abuse, it is highly likely that this drug or substance shares subjective effects with reference drug and would be similarly abused by humans.

Animals trained to discriminate the presence versus absence of morphine-like μ opioid receptor agonists 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 ED50 values for cross-generalization with the 3 mg/kg morphine training cue in these rats with 30 and 60 minutes 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 subcutaneously (SC) administered morphine (3.2 mg/kg, prior to each session) and trained to discriminate
naltrexone (0.01 mg/kg, SC) from vehicle. Hydrocodone (ED50 = 0.37 mg/kg), 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. These 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 milligrams/kilograms (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. Conditioned place preference

Nazarian and his associates (2011) studied the rewarding effects of hydrocodone, acetaminophen and their combination using a 6-day conditioned place preference paradigm in rats. These authors found that rats conditioned with intraperitoneally (IP) administered hydrocodone (5 mg/kg), similar to morphine (5 mg/kg IP), exhibited place preference, while rats conditioned with varying doses of acetaminophen (50, 100 or 300 mg/kg, IP) did not show place preference. Various doses of acetaminophen (50, 100 or 300 mg/kg, IP) in combination with hydrocodone (5 mg/kg, IP) did not alter the hydrocodone’s conditioned place preference with the exception of the combination of 100 mg/kg acetaminophen with 1 mg/kg hydrocodone which led to significant conditioned place preference. The 1 mg/kg hydrocodone alone did not produce conditioned place preference. However, this combination of 100 mg/kg acetaminophen and 1 mg/kg hydrocodone did not result in enhancement of hydrocodone-induced locomotor activity. Acetaminophen did not attenuate the hydrocodone-induced conditioned place preference. These authors concluded that the acetaminophen, the most common constituent of prescription opioid analgesic products, does not seem to contribute to the rewarding effects of hydrocodone containing prescription opioid analgesic products.
Tenayuca and Nazarian (2012) reported that rewarding effects of hydrocodone (5 mg/kg) are similar to that of morphine (5 mg/kg) as assessed by conditioned place preference tests in rats. Hydrocodone, similar to morphine, reduced phosphorylation of both extracellular signal-related kinases (ERK) and of its downstream transcription factor, cyclic-AMP response element binding protein (CREB) in rat nucleus accumbens. Both ERK and CREB are known to be critical signal transduction markers for drug reward and reinforcement. These authors concluded that hydrocodone is similar to morphine in producing rewarding effects and signal transduction changes.

1.1.1.4. Morphine-like withdrawal effects

Deneau and 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 the results obtained in humans (Seevers and Deneau, 1956).

In 1959, Deneau, McCarthy, and 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. These authors found that hydrocodone is more potent than morphine in suppressing morphine abstinence in monkeys and equipotent to morphine in humans.

Preclinical studies 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. Acetaminophen, the most common nonnarcotic ingredient in hydrocodone containing prescription opioid analgesics, does not attenuate the rewarding effects of hydrocodone as assessed by conditioned place preference method, instead at a particular dose enhances its reward. These data collectively suggest that hydrocodone has an abuse liability similar to morphine.
1.1.2. Abuse liability: Clinical studies

1.1.2.1. Hydrocodone

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 codeine 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 (administered 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.

Stoops and his associates (2010) conducted a double-blind, randomized, with-in subject, placebo-controlled clinical study in subjects with recreational opioid use and histories of intravenous opioid use to investigate the relative abuse potential of intravenously administered (5, 10 and 20 mg) oxycodone hydrochloride, morphine sulfate and hydrocodone hydrochloride. These authors found that all three opioids produced in general dose-dependent μ opioid receptor agonist effects (e.g., miosis, increased ratings of drug liking and good effects). There were no differences in the time-course and peak effects across these three opioid analgesics. There were small potency differences between oxycodone and hydrocodone in comparison to morphine. The average potency of morphine relative to oxycodone and hydrocodone were 1.03 and 0.92, respectively. In light of these results and the previously published findings by Zacny and his associates indicating the inability of acetaminophen present in opioid combination products to alter its abuse potential, these authors suggested that clinician prescribers should prescribe HCPs with the same degree of caution as with schedule II opioids.

1.1.2.2. HCPs

The HHS 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. The HHS review cited the following clinical rationale for the current less restrictive schedule of HCPs (schedule III) as compared to hydrocodone substance (schedule II). The 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 analgesic present in these combination products is thought to occur. DEA notes that 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 HCPs contain nonnarcotic substance that is not analgesic (e.g. Hycodan® containing homatropine). Thus the above rationale of analgesia potentiation does not apply to all HCPs. The HHS further postulates that the nonnarcotic active ingredient present in HCPs could lower the abuse potential of these products through its toxic, dysphoric, and unpleasant effects if high doses of these products are ingested.

The HHS reviewed a double-blind, randomized placebo-controlled crossover clinical study by Zacny (2003) who showed that Hycodan®, a HCP containing homatropine, produced both pleasant and unpleasant effects in volunteers with history of recreational drug use, but no history of drug dependence. The HHS further postulated from these findings by suggesting that unpleasant effects of nonnarcotic active ingredient present in this combination product may limit its abuse potential. However, the DEA notes that Zacny (2003) further stated that the subjective effects (both pleasant and unpleasant effects) of HCP, Hycodan®, are similar to those of morphine and other μ opioid agonists. In this study 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. Morphone 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. 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.

Zacny et al. (2005) using a double-blind, randomized placebo-controlled crossover clinical 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 HCP (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 HCP (20 mg hydrocodone/1000 mg acetaminophen) and morphine impaired psychomotor performance and produced miosis. 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. These authors concluded that abuse liability-related subjective effects of hydrocodone/acetaminophen combination product are in accordance with the widespread nonmedical use and abuse of this combination product.

The DEA notes another double-blind, randomized placebo-controlled crossover clinical study by Zacny and Gutierrez (2009) who studied the comparative psychopharmacological profile of orally administered placebo, acetaminophen (975 mg), and acetaminophen (487 and 975 mg) in combination with hydrocodone (15 and 30 mg) or in combination with oxycodone (10 and 20 mg) in non-drug-abusing human volunteers with some history of recreational drug use but without a history of substance use-related disorders. These authors found that acetaminophen did not differ from placebo in all measures. Hydrocodone/acetaminophen and oxycodone/acetaminophen combination products at equi-miotic doses, in general, produced similar profile of psychopharmacological effects. These two opioid products produced prototypic opiate-like effects and psychomotor impairment of similar magnitudes. These findings with hydrocodone/acetaminophen and oxycodone/acetaminophen combination products are almost identical to those reported for the single-entity products containing hydrocodone and oxycodone (Walsh et al., 2008).

The DEA notes another double-blind placebo-controlled crossover clinical study by Wilsey et al. (2009) who evaluated the abuse liability of extended release morphine (15 mg) and the combination of hydrocodone (30 mg) and acetaminophen (975 mg) in chronic pain patients with history of prescription opioid abuse. These authors found that effects of these two drugs on the markers of drug liking/abuse liability did not significantly differ from each other.

Abuse liability: clinical studies - 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 humans. Hydrocodone, similar to morphine, produces opioid withdrawal syndrome. HCPs (Hycodan® or hydrocodone in combination with acetaminophen) are similar to morphine with respect to physiological effects, subjective effects, and “liking” scores. Hydrocodone/acetaminophen and oxycodone/acetaminophen combination products at equi-miotic doses, in general, produce similar profile of psychopharmacological effects. These two opioid products produced prototypic opiate-like effects and psychomotor impairment of similar magnitudes. Acetaminophen, the nonnarcotic analgesic ingredient present in majority of the currently marketed HCPs, at clinically relevant doses lacks psychoactive effects.

Abuse liability studies - summary

In summary, hydrocodone, similar to morphine, is a µ opioid receptor agonist and shares pharmacological properties with morphine. Hydrocodone substitutes for morphine in animals trained to discriminate the presence and absence of morphine. Hydrocodone, similar to morphine, is self-administered by animals. 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 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 HCPs 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 basis for placing HCPs in schedule III. On the contrary, the recent clinical studies found that the abuse liability related subjective effects of HCPs, namely Hycodan® and hydrocodone in combination with acetaminophen, are similar to those of morphine, a schedule II opioid analgesic, and oxycodone/acetaminophen combination. These clinical studies and the actual abuse as presented in the following section suggest that the potential for abuse of HCPs 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 marketed19, 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 evidence of clandestine production of these substances. DEA does not have evidence that either drug products are illicitly imported into the U.S. in any significant amounts. The production and prescription of

19 In the United States there are currently no approved, marketed, products containing hydrocodone in combination with other active ingredients that fall outside schedule III of the CSA. Further, until recently, there were no approved hydrocodone single-entity schedule II products. In Oct. 2013, the FDA approved Zohydro™ ER, a single-entity, extended release schedule II hydrocodone product. The sponsor of this product in a press release dated Oct. 25, 2013 stated that Zohydro™ ER will be launched in approximately four months. Accordingly, all of the historical data regarding hydrocodone from different national and regional databases that support this proposal should refer to HCPs only, regardless of whether the database utilizes the term “hydrocodone” or “hydrocodone combination products.”
these products have increased dramatically in recent years. Various data sources indicate that HCPs as well as oxycodone products are extensively diverted and abused and are associated with considerable morbidity/mortality.

As mentioned above, the term “abuse” is not defined in the CSA. However, the legislative history of the CSA suggests a four-criterion approach in determining whether a particular drug or substance has a potential for abuse. Data for HCPs and oxycodone products as applied to each of these four criteria are presented below.

1.2.1. Analysis methods used in the current evaluation

Before presenting the data, the issues related to methodology used in the current evaluation needs to be taken into account in order to draw reasonable conclusions from these data. The important aspects to consider in performing a comparative evaluation of epidemiological data are the following: (i) the selection of most appropriate reference drug; (ii) the choice of numerator to calculate abuse rates; (iii) the selection of appropriate denominator to calculate abuse rates. These are discussed below.

1.2.1.1. The selection of the most appropriate reference drug

In evaluating a drug or substance for control under the CSA, the data for the same is typically compared with the data for a reference drug or a substance from the same pharmacological class as the test drug or substance. The HHS examined this issue. Based on similarities between HCPs and oxycodone products with regard to their pharmacological properties, market history, and the patterns and indications for use, HHS concluded that oxycodone products are the most appropriate comparator drugs for evaluating HCPs and thus used the same in its scientific and medical evaluation.

The HHS stated that there is no suitable schedule III opioid drug for use as reference opioid drug for evaluating HCPs. Further, the HHS mentioned that codeine products are also not appropriate for comparison for the following reasons: (i) Codeine products are controlled under three different schedules (schedules II, III and IV) and schedule-specific codeine data is not possible to obtain; (ii) Clinical use of codeine-containing products is substantially less than the use of HCPs; (iii) Codeine products are subjected to additional state-specific stronger restrictions than the CSA regulations and thus difficult to draw general conclusions from using such data; (iv) Codeine-specific data suffer from serious deficiencies for several other reasons. For the above reasons, the HHS evaluated the abuse liability of HCPs by comparing with oxycodone products (schedule II).
Although oxycodone products are the best available comparator drugs, it is important to note that hydrocodone is marketed as combination (low strength immediate release) products whereas oxycodone products are marketed as both single-entity (medium strength immediate release and high strength extended release products) and combination (low strength immediate release) products in the U.S. (all oxycodone products are controlled as schedule II under the CSA). Of particular concern are the high-strength single-entity extended release oxycodone products and these products contain up to 80 mg oxycodone (160 mg formulation was initially marketed, but subsequently it was taken off the market for safety concerns) and these are several-fold higher than the maximal amount present in its combination products (10 mg) and the maximal amount of hydrocodone present in HCPs (10 mg). Oxycodone single-entity immediate release products contain up to a maximum of 30 mg oxycodone. Thus the oxycodone combination products, without the inclusion of its single-entity immediate release and extended release products, are better comparator drugs for the present evaluation of HCPs. The DEA further notes that this comparison can be further improved by selecting the products of similar strengths (mg/unit) of HCPs versus oxycodone products. However, such analyses largely are not possible, because majority of currently available drug abuse databases do not provide product-, formulation- (immediate release versus extended release), composition- (single-entity versus combination products) and strength-specific data. However, DEA obtained limited product-specific data for OxyContin®, an extended release oxycodone product and accordingly evaluated with and without the inclusion of OxyContin®-specific data and presented as appropriate in this document.

1.2.1.2. The choice of numerator to calculate abuse rates

Some drug abuse databases provide only partial data due to certain database-specific limitations and such limitations need to be taken into account while using these data as numerators to calculate rates of abuse of a given product at the national level. For example, as stated in the HHS review, the data for OxyContin®, and Vicodin® as reported in the Monitoring the Future (MTF) (a survey of high school students about nonmedical use of drugs) cannot be used as full representations for oxycodone products and hydrocodone products, because there are various HCPs other than Vicodin® and many oxycodone products other than OxyContin®.

Another example of a database that reports data partially is the Treatment Episode Data Set (TEDS), a database reporting data on admissions to drug addiction treatment facilities. The HHS states that the TEDS includes data collected by states primarily from the addiction treatment facilities that receive public funds. TEDS data is reported with two levels of detail: (i) a Minimum Data Set collected by all states, and (ii) a Supplemental Data Set collected by some

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20 According to the FDA briefing document of the Drug Safety and Risk Management Advisory Committee meeting, (held on January 24-25, 2013), the term “abuse ratio” is more appropriate than the “abuse rate.” In this document, these terms are used interchangeably. As discussed in the FDA’s briefing document, the inability to calculate confidence intervals around estimated prevents from subjecting these abuse rates for statistical comparison between hydrocodone products and oxycodone products. The FDA briefing document further states the following: “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 best of our ability in this review.”
states only. All states and jurisdictions are required to report the Minimum Data Set that includes narcotic analgesics-related admissions data under a single response category titled “Opiates other than Heroin.” This category included methadone, codeine, hydrocodone, hydromorphone, meperidine, morphine, opium, oxycodone, pentazocine, propoxyphene, tramadol, and any other drug with morphine-like opioid properties, excluding heroin and the nonprescription use of methadone. The Supplemental Data Set provides a more detailed listing of the substance problem (primary, secondary, and tertiary drug) and reports substance-specific information for codeine, hydrocodone, hydromorphone, meperidine, morphine, opium, oxycodone, pentazocine, propoxyphene, tramadol, and “Other opiates and synthetics.” States and jurisdictions can choose whether or not to report the narcotic analgesic substance-specific detailed reports. Thus, as stated by the HHS the narcotic analgesic substance-specific TEDS data are limited. Thus the data for oxycodone and hydrocodone as reported in the TEDS cannot be used as full representations for all oxycodone products and HCPs. Thus these data cannot be used to calculate rates of narcotic analgesic-related addiction treatment admissions at the national level.

Another example of a database that reports data partially is the ME data reported by the DAWN database. DAWN monitors drug-related deaths referred to medical examiners and coroners in selected metropolitan areas and states. A DAWN ME case is any drug use related death as determined by the Medical Examiner or Coroner. As stated in the HHS review, the ME data reported by the DAWN database are limited and do not represent national estimates of drug-related deaths. These data cannot be used to calculate rates of drug-related deaths at the national level.

1.2.1.3. The choice of denominator to calculate abuse rates

There is a considerable discussion among epidemiologists about the selection of appropriate denominator (representing drug availability for abuse) in calculating 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. As stated by the HHS, while calculating abuse rates, in the past, the DEA and the HHS have used one or more of the following denominators as representation of availability of drug (for diversion and abuse). These include: (i) Total U.S. population; (ii) Total number of prescriptions; (iii) Total patient days of therapy; (iv) Total amount of substance distributed (in kilograms); (v) Total number of extended units (i.e. pills or tablets) dispensed; (vi) Total number of patients receiving a dispensed prescription.

The HHS states that no single denominator adequately reflects the amount of HCPs and oxycodone products available in the market place to allow the inter-drug comparisons, while also taking into account in full the differences in composition, formulation, quantity of substance dispensed and the amount of active drug in each dosage unit dispensed. According to the HHS, each of the denominators offers specific advantages, and the use of each different denominator produces different results when comparing HCPs versus oxycodone products. The FDA has considered various denominators and discussed in detail their strengths and limitations at the
FDA Advisory Committee meeting held on January 24-25, 2013 (see FDA Briefing Document: Drug Safety and Risk Management Advisory Committee meeting, January, 2013). After examining various denominators, the FDA concluded in its briefing document that “Total number of extended units dispensed” as a denominator provided the best metric of patient exposure-based risk while the “total amount of substance distributed” as a denominator is likely the best metric to assess population exposure-based risk. According to the FDA, the “total number of extended units dispensed” as a denominator reflects adequately for the variability in the numbers of dosage units dispensed per prescription between hydrocodone and oxycodone products and it also takes into account the differences specific to product formulation and composition. Thus, HHS, in addition to the total prescriptions as used in its previous (provided to the DEA in 2008) evaluation document, also used this metric of “Total number of extended units dispensed” as a denominator to calculate rates and presented the same in its current evaluation.

However, it is important to note that HCPs are available as combination (low strength immediate release) products only whereas oxycodone products are available as both single-entity (medium strength immediate release and high strength extended release products) and combination (low strength immediate release) products in the U.S. As discussed earlier the oxycodone extended release products contain up to a maximum of 80 mg oxycodone (160 mg formulation was initially marketed, but subsequently it was taken off the market for safety concerns) that is several multiples of its analgesic dose equivalents present in its immediate release combination products (a maximum of 10 mg) and in its immediate release single-entity products (a maximum of 30 mg) and in HCPs (a maximum of 10 mg). Because abuse-related adverse consequences such as ED admissions, deaths and abuse/dependence properties of a given drug are primarily dependent on the dose (i.e., higher the dose amount the greater the likelihood of toxicity resulting in morbidity and mortality), it is important to take into account these differences in drug amounts per dose unit between HCPs and oxycodone products while assessing the relative abuse potential. Although it is difficult to fully and precisely account for these differences in drug amounts, as discussed below, the DEA believes that the use of the average drug amount per extended unit as an additional denominator is an improved metric to assess relative abuse potential and it can further the HHS analyses.

The average drug amount per each extended unit can be calculated by dividing the total amount (in kilograms) of drug distributed to pharmacies by the total number of extended units (pills) for the same drug distributed to pharmacies. The DEA utilized data from the National Sales Perspective™ (NSP™), a database of IMS Health Inc, to calculate the average drug amount per each extended unit for HCPs and for oxycodone products (Table 1). These analyses found that the average amount of hydrocodone present in each extended unit of HCPs marketed during 1998 through 2012 gradually increased and ranged from a minimum of 6.687 mg (in 1998) to a maximum of 7.713 mg (in 2012). The average amount of oxycodone present in each extended unit of all oxycodone products (both immediate release single-entity and combination products and extended release single-entity) marketed during 1998 through 2012, with the exception of years 2011 and 2012, also gradually increased and ranged from a minimum of 8.091 mg (in 1998) to a maximum of 14.548 mg (in 2010) (Table 1). Thus oxycodone products on average contained larger drug amount per each of its extended unit dispensed compared to that of HCPs during 1998 to 2012. In 2012, the average amount of oxycodone present in each unit of all oxycodone products was nearly twice that of the average amount of hydrocodone present in each
Temporal increases in drug amount per unit of oxycodone products (a 75% increase from 1998 through 2012) were markedly higher than the corresponding increases reported for HCPs (15% increase from 1998 through 2012). Because abuse-related adverse health outcomes are dependent on the drug amount (i.e., higher the drug amount greater the likelihood of morbidity and mortality), it is important to take into account these differences while performing a comparative evaluation of HCPs with oxycodone products.

Further there are formulation-specific differences in the average drug amounts per unit among different formulations of oxycodone products distributed. For example, the average amount of oxycodone present in each extended unit of oxycodone immediate release (both single-entity and combination) products marketed during 1998 through 2012 gradually increased and ranged from a minimum of 4.99 mgs (in 1998) to a maximum of 11.39 mgs (in 2011). The average amount of oxycodone present in each extended unit of oxycodone extended release single-entity products marketed during 1998 through 2012, with the exception of years 2011 and 2012, also gradually increased and ranged from a minimum of 24.83 mgs (in 1998) to a maximum of 40.78 mgs (in 2010).

In light of the above considerations, the DEA applied the “average drug amount per extended unit”, derived from IMS Health’s NSP™ database, as an additional denominator to normalize the rates obtained from using “total extended units dispensed” as the denominator and the resultant rates are mentioned as appropriate in this document. Hydrocodone bitartrate is equipotent to oxycodone hydrochloride on mg basis as oral analgesic (HHS review document; Gutstein and Akil, 2006). Similarly clinical studies showed that oral hydrocodone bitartrate has been shown to be approximately equipotent to or slightly less potent than oxycodone hydrochloride on mg basis in producing abuse liability related subjective effects profile (Walsh et al., 2008). Because these data indicate that both hydrocodone bitartrate and oxycodone hydrochloride are approximately equipotent, the average mg quantities of drugs present in each extended unit of HCPs and oxycodone products were used as denominators in calculating rates. The results of these analyses are presented in the current review document. This expanded analysis as presented later in this document largely showed that the HCPs have high potential for abuse similar to that of schedule II oxycodone products.
<table>
<thead>
<tr>
<th>Year</th>
<th>HCPs</th>
<th></th>
<th>Oxycodeone products</th>
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<tr>
<td></td>
<td>Total quantity (kgs)</td>
<td>Total number of extended units (pills) (millions)</td>
<td>Average drug amount (mgs) per extended unit</td>
</tr>
<tr>
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<td>15,359.4</td>
<td>2,296.9</td>
<td>6.687</td>
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<td>1999</td>
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<tr>
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</tr>
<tr>
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<tr>
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</tr>
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<td>2012</td>
<td>63,338.1</td>
<td>8,212.0</td>
<td>7.713</td>
</tr>
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</table>

The data were extracted on January 6, 2014.

Over 92 to 98% of all HCPs was marketed as solid dosage formulations during 2002 through 2012, while about 99% of all oxycodone products was marketed as solid dosage formulations. Therefore the total quantity (in kilograms) of HCPs and oxycodone products presented in the table are for the corresponding solid dosage formulations. Similarly the total numbers of extended units shown in the table are for the solid dosage formulations.

According to the FDA’s briefing document for Advisory Committee meeting held on January 24-25, 2013, population exposure-based and patient exposure-based drug abuse-related adverse health outcome rates can be calculated by using population exposure-based denominators (i.e., U.S. population, and total amount of substance distributed) and patient exposure-based denominators (i.e., prescriptions, extended units, total number of patients), respectively. These are important metrics to consider in the evaluation of public health impact and risk profile of HCPs. The FDA further states that population exposure-based rates can be used to evaluate a product’s abuse/misuse risk profile from a community perspective while patient exposure-based rates provide a metric to evaluate abuse/misuse risk from a patient’s perspective. The use of “total extended units dispensed” as a denominator to calculate rates is likely the best metric to assess the patient exposure-based risk, while the “total amount of substance distributed” as a denominator is likely the best metric to assess the population.
exposure-based risk. Thus, the DEA also utilized the total amount of substance distributed, obtained from Automation of Reports and Consolidated Orders System (ARCOS)\textsuperscript{21} database, as the denominator to calculate abuse rates and the results are presented as appropriate.

1.2.2. Criterion 1: 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

The data from several sources as presented below indicate that abuse of HCPs and oxycodone products is widespread in the U.S. and the abuse of these products is associated with considerable morbidity and mortality. These adverse health consequences resulting from abuse of HCPs are largely similar to those of oxycodone products (schedule II) products. These data are presented below.

1.2.2.1. DAWN data

The DAWN is a public health surveillance system that monitors drug abuse-related ED visits to hospitals and drug-related deaths reported by medical examiners and coroners participating in the DAWN. The Substance Abuse and Mental Health Administration (SAMHSA) is the federal agency responsible for DAWN operations. The DAWN data are used to track the impact of drug use, misuse, and abuse in the U.S.

1.2.2.1.1. DAWN emergency department (ED) data

The HHS review states that to analyze ED visits related to misuse and abuse of pharmaceuticals, the SAMHSA uses the metric namely “nonmedical use of pharmaceuticals” (NMUP). This metric combines ED visits related to the use of drug in amounts exceeding the prescribed or recommended dose, the use of drugs prescribed for another person, malicious poisoning, or substance abuse.

The HHS also states that to evaluate the relative abuse potential of a drug it is important consider both the absolute number of events and the rates at which such events occur. As mentioned previously, following consideration of various denominators, the HHS concluded that the “total tablets (otherwise called Extended Units) dispensed “is the most appropriate denominator to estimate “abuse ratios” and used it to calculate rates as the number of NMUP ED visits per million tablets dispensed. According to the HHS, these rates are the best metric to assess the patient exposure-based risk. Using this analytical approach, the HHS evaluated the

\textsuperscript{21}The Automated Reports and Consolidated Orders System (ARCOS), a database of DEA, enables to monitor the distribution of substances throughout the country, and to identify retail level registrants that receive unusual quantities of controlled substances. The CSA mandates that manufacturers submit periodic reports of the Schedule I and II controlled substances they produce in bulk and dosage forms. They also report the manufactured quantity and form of each narcotic substance listed in Schedule III. Distributors of controlled substances must report the quantity and form of all their transactions of controlled drugs listed in Schedules I and II, narcotics listed in Schedule III, and gamma-hydroxybutyric acid. Both manufacturers and distributors are required to provide reports of their annual inventories of these controlled substances. These data are entered into ARCOS. The total sale of each of these drugs in grams recorded in ARCOS is a representation of its quantities legitimately distributed to retail level such as pharmacies, hospitals and practitioners.
DAWN data from 2004 through 2011 for HCPs and oxycodone products and found that the nonmedical use of both these drugs are linked to large numbers of ED visits.

The HHS found that the nonmedical use of HCPs, similar to oxycodone products, have been associated with large numbers of annual ED visits from 2004 through 2011. The HHS using the total number of extended units as the denominator found that the rates of ED visits related to NMUP for oxycodone products were higher than the corresponding rates for HCPs. The HHS further found that these rates for oxycodone products continue to increase, whereas the rates for HCPs, while considerable, appear to have leveled off in the most recent years. However, the HHS states that the magnitude of adverse effects (both in the actual number of individuals affected and the severity of adverse effects suffered by individuals) associated with HCPs is large and is indicative of its high abuse potential. For example, the HHS mentions that in 2011, there were 82,479 ED visits associated with abuse of HCPs. HCPs contributed to substantial numbers of overdose deaths each year. The ED visits and mortality data for HCPs are showing increasing trend. Prescriptions for each year for HCPs, unlike any other opioid product, are large and unprecedented. According to the HHS this characteristic drives the potential for abuse and sets HCPs apart from any other opioids in terms of risk for abuse. The negative public health result for both HCPs and oxycodone products are considerable.

For the reasons mentioned earlier, the DEA expanded the HHS analyses using average drug amount (in mgs) present in an extended unit of HCPs and oxycodone products as an additional denominator to calculate rates. The DAWN data indicate that from 1998 through 2002, annual mentions of ED visits related to nonmedical use of HCPs consistently exceeded those for oxycodone products, while from 2004 through 2011, this trend was reversed (Table 2). DEA finds that rates of ED visits, calculated as the number of ED visits per million extended units, for oxycodone products are higher (about 3- to 4-fold) than the corresponding rates for HCPs. However, when the differences in drug amounts in extended units of HCPs versus oxycodone products were taken into account (by dividing the above rates with average mg drug amounts per extended unit data as denominator), the differences between HCPs and oxycodone products were substantially reduced (to 1.2 to 2.2-fold). As mentioned before, ideal comparison is between oxycodone combination products, but not all oxycodone products, and HCPs. However, such analyses currently are not possible as the formulation-specific ED visits data are not available.

Contrary to the rates obtained using extended units dispensed as the denominator, the rates of ED visits per kilogram of HCPs versus oxycodone products distributed did not show consistent differences. For example, from 1998 through 2000 the rates for HCPs were slightly higher than the corresponding rates for oxycodone products, while these were similar in 2001. From 2002 through 2011, the rates for HCPs were lower compared to oxycodone products. The present results, especially prior to 2002, obtained from using ARCOS drug distribution data as a denominator are in general consistent with those reported by Dasgupta et al. (2006). These authors used retail drug distribution amounts (as reported by IMS Health’s NSP™) as a denominator and found that annual morbidity rates, calculated as annual ED mentions (as reported in DAWN from 1994 through 2002) per each kilogram of drug distributed, for a number of opioid analgesics including HCPs and oxycodone products, when adjusted for relative potency differences, did not considerably differ from each other.
Table 2. Nonmedical use related (NMUP) ED visits (DAWN*) for HCPs and oxycodone products. Rates of ED visits are calculated using extended units dispensed, extended units/mg/unit, and kilograms (kg)# distributed as denominators.

<table>
<thead>
<tr>
<th></th>
<th>HCPs</th>
<th></th>
<th></th>
<th></th>
<th>Oxycodone products</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NMUP ED visits</td>
<td>EDs/million extended units</td>
<td>EDs/million extended units/mg/unit</td>
<td>EDs/kg</td>
<td>NMUP ED visits</td>
<td>EDs/million extended units</td>
<td>EDs/million extended units/mg/unit</td>
<td>EDs/kg</td>
</tr>
<tr>
<td>1998</td>
<td>13,611</td>
<td>3.47</td>
<td>0.52</td>
<td>0.80</td>
<td>5,211</td>
<td>6.91</td>
<td>0.85</td>
<td>0.71</td>
</tr>
<tr>
<td>1999</td>
<td>15,252</td>
<td>3.26</td>
<td>0.48</td>
<td>0.77</td>
<td>6,429</td>
<td>6.72</td>
<td>0.68</td>
<td>0.60</td>
</tr>
<tr>
<td>2000</td>
<td>20,098</td>
<td>4.00</td>
<td>0.58</td>
<td>0.87</td>
<td>10,825</td>
<td>8.83</td>
<td>0.73</td>
<td>0.64</td>
</tr>
<tr>
<td>2001</td>
<td>21,567</td>
<td>3.86</td>
<td>0.56</td>
<td>0.84</td>
<td>18,409</td>
<td>12.63</td>
<td>0.95</td>
<td>0.83</td>
</tr>
<tr>
<td>2002</td>
<td>25,197</td>
<td>4.13</td>
<td>0.59</td>
<td>0.82</td>
<td>22,397</td>
<td>13.30</td>
<td>1.00</td>
<td>0.90</td>
</tr>
<tr>
<td>2004*</td>
<td>39,844</td>
<td>5.84</td>
<td>0.81</td>
<td>1.01</td>
<td>41,701</td>
<td>24.77</td>
<td>1.87</td>
<td>1.29</td>
</tr>
<tr>
<td>2005</td>
<td>47,192</td>
<td>6.92</td>
<td>0.96</td>
<td>1.12</td>
<td>52,943</td>
<td>24.78</td>
<td>1.89</td>
<td>1.56</td>
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<td>2006</td>
<td>57,550</td>
<td>7.46</td>
<td>1.02</td>
<td>1.18</td>
<td>64,888</td>
<td>27.16</td>
<td>2.02</td>
<td>1.58</td>
</tr>
<tr>
<td>2007</td>
<td>65,735</td>
<td>8.12</td>
<td>1.10</td>
<td>1.22</td>
<td>76,587</td>
<td>28.04</td>
<td>2.04</td>
<td>1.60</td>
</tr>
<tr>
<td>2008</td>
<td>89,051</td>
<td>10.39</td>
<td>1.40</td>
<td>1.52</td>
<td>105,214</td>
<td>34.22</td>
<td>2.47</td>
<td>1.93</td>
</tr>
<tr>
<td>2009</td>
<td>86,258</td>
<td>10.24</td>
<td>1.37</td>
<td>1.38</td>
<td>148,449</td>
<td>42.87</td>
<td>3.03</td>
<td>2.39</td>
</tr>
<tr>
<td>2010</td>
<td>95,972</td>
<td>11.32</td>
<td>1.49</td>
<td>1.49</td>
<td>146,355</td>
<td>38.94</td>
<td>2.68</td>
<td>2.06</td>
</tr>
<tr>
<td>2011</td>
<td>82,480</td>
<td>9.52</td>
<td>1.25</td>
<td>1.18</td>
<td>151,218</td>
<td>35.24</td>
<td>2.51</td>
<td>2.13</td>
</tr>
</tbody>
</table>

# Data for the total kilograms of drug distributed annually were obtained from ARCOS.
Ω Data for the total extended units dispensed annually were obtained from the IMS Health, IMS Health Nationals Prescription Audit™ (NPA™)
*Changes in DAWN methodology were implemented in 2003 and thus the data from 2004 through 2011 cannot be compared to those of the previous years.

1.2.2.1.2. ME data

DAWN also monitors drug-related deaths referred to medical examiners and coroners in selected metropolitan areas and states. As the HHS mentioned, the DAWN ME data are not national estimates and cannot be trended. Thus it is not possible to calculate the rates for these data at the national level. However, the HHS reviewed the DAWN ME data for five states and found that from 2004 through 2010 the number of deaths related to HCPs and oxycodone products increased by 63% and 133%, respectively. Total number of deaths attributed to oxycodone products was higher than that for HCPs.

In summary, DAWN ED visits and ME data suggest that both HCPs and oxycodone products have large adverse impact on public health as both these products caused large numbers of nonmedical use related ED visits and deaths.
1.2.2.2. 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. The NPDS tracks the number of drug- or substance-related calls to poison centers. The HHS reviewed the data from 2002 through 2011 for HCPs and oxycodone products and found that the number of toxic exposures involving HCPs exceeded the corresponding exposures for oxycodone products. The total number of toxic exposures for HCPs increased from 17,429 in 2002 to 30,792 in 2011. Similarly the total number of toxic exposures for oxycodone products rose from 10,515 in 2002 to 19,423 in 2011.

The DEA further notes that according to the annual reports of NPDS in recent years, annual figures for toxic exposures (within the category of opioid analgesic drugs) were the largest for HCPs, followed by oxycodone products (Watson et al., 2003, 2004, 2005; Lai et al., 2006; Bronstein et al., 2007, 2008, 2009, 2010, 2011, 2012; Mowry et al., 2013). Table 3 provides annual toxic exposures mentioning HCPs and oxycodone products and associated deaths from 2001 through 2012. Majority of exposures for both drug products were for intentional reason. The DEA also notes that toxic exposures to HCPs and oxycodone products are associated with fatalities. Cumulative total deaths from 2001 through 2005 associated with all exposures to HCPs (382 deaths) were larger than that associated with all exposures to oxycodone products (316 deaths). Cumulative total deaths from 2006 through 2012 associated with single substance exposures to HCPs (195 deaths) were slightly higher than that associated with single substance exposures to oxycodone products (173 deaths).

The HHS calculated rates of toxic exposures using total extended units (tablets) and prescriptions dispensed as denominators and found that rates for HCPs ranged between 4.5 and 3.5 exposures per million tablets dispensed from 2002 and 2011. The corresponding numbers for oxycodone products were 6.8 and 4.3. Using prescriptions as denominator, the HHS reported that the rates for HCPs ranged between 1.8 and 2.4 exposures per ten thousand prescriptions dispensed from 2002 and 2011. The corresponding numbers for oxycodone products were 3.3 and 4.1.
Table 3. Annual reported toxic exposure cases involving HCPs and oxycodone products (NPDS)§

<table>
<thead>
<tr>
<th>Year</th>
<th>Total toxic exposure cases</th>
<th>Single substance exposure cases</th>
<th>Fatalities</th>
<th>Total toxic exposure cases</th>
<th>Single substance exposure cases</th>
<th>Fatalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>15,191</td>
<td>9,480</td>
<td>54</td>
<td>10,515</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>17,429</td>
<td>11,254</td>
<td>60</td>
<td>12,603</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>19,578</td>
<td>13,191</td>
<td>78</td>
<td>13,473</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>22,654</td>
<td>15,069</td>
<td>13</td>
<td>17,256</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>22,229</td>
<td>13,191</td>
<td>22</td>
<td>19,363</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>22319</td>
<td>10,061</td>
<td>17</td>
<td>13,473</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>24,558</td>
<td>11,001</td>
<td>23</td>
<td>15,069</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>26,306</td>
<td>12,559</td>
<td>31</td>
<td>18,396</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>27,753</td>
<td>12,541</td>
<td>30</td>
<td>19,363</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>28,310</td>
<td>13,756</td>
<td>37</td>
<td>19,377</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>30,792</td>
<td>13,046</td>
<td>36</td>
<td>18,495</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

*Changes in reporting were implemented in 2006.

§In the U.S., nearly 100% of total kilogram amounts of HCPs 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).

#Beginning in 2006, fatalities mentioned are deaths resulting from single substance exposures.

For the reasons mentioned earlier, the DEA further expanded the HHS analyses using average drug amount (in mgs) present in an extended unit of HCPs and of oxycodone products as an additional denominator to calculate rates. Similar to the findings of the HHS, the DEA found that the rates of toxic exposures for oxycodone products calculated as the annual total exposure cases per million extended units are higher (from 1.2 to 2.2-fold) as compared to the corresponding rates of exposures for HCPs from 2001 through 2012 (Table 4). However, when the differences in drug amounts in extended units of HCPs versus oxycodone products were taken into account (by dividing the above rates with average mg drug amounts per extended unit data as denominator), the rates of annual toxic exposures to HCPs were largely similar to those of oxycodone products. Contrary to the rates obtained using extended units dispensed as the denominator, the rates of toxic exposures per kilogram of HCPs were slightly higher than that of oxycodone products distributed (Table 4). As mentioned before, ideal comparison is between HCPs and oxycodone combination products, but not all oxycodone products. However, due to lack of formulation-specific toxic exposure data, such analyses are not possible.

In summary toxic exposures data from poison centers suggest that both HCPs and oxycodone products have large adverse impact on public health as both these products are associated with large numbers of toxic exposures and deaths. Annual toxic exposures involving HCPs exceeded the corresponding exposures for oxycodone products from 2002 through 2012. The relative toxicity potential per kilogram of HCPs distributed is slightly higher than that of
oxycodone products. Toxic exposures to both HCPs and oxycodone products are associated with deaths.

The DEA further notes that Hughes et al. (2007) collected and analyzed data about prescription opioid-related intentional exposure (abuse, intentional misuse, suicide, or intentional unknown reasons) 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 and compared these data to drug-related ED visits data (from DAWN). These authors selected the intentional exposure call category for use as a surrogate for possible abuse and misuse. These authors cited the following reasons as the basis for the selection of DAWN as a comparator database: 1) the majority of intentional exposures calls to the poison control centers regarding these drugs are from health care providers/health care facilities. DAWN collects information from drug-related emergency department visits and thus provides a similar comparison population; 2) DAWN’s (pre-2003) description of abuse is analogous to the poison center intentional exposure category. DAWN (pre-2003) defines drug abuse as a “nonmedical use of a substance for psychic effect, dependence, suicide attempt/gesture, or the use of prescription drugs in a manner that is inconsistent with the accepted medical practice”. These authors found that the comparison of poison control centers data to that of DAWN yielded in general similar results including analogous proportions of abuse and misuse by gender, and the high numbers of cases involving both HCPs and oxycodone products. These authors concluded that poison centers data can be used as an indicator for prescription opioid abuse and misuse. Several other studies that used intentional exposures as surrogate for abuse and misuse have been published recently (Smith et al., 2007; Dart et al., 2012; Spiller et al., 2010; Zosel et al., 2013).

Similarly, Davis and his associates (2013) compared the population rates of poison center call mentions regarding abuse and misuse of prescription opioids (buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, and oxycodone) with population rates of ED visit mentions of the same using linear regression. These authors found a strong correlation between the two programs using the data from 2004 through 2010. These authors concluded that due to timeliness of data, geographic coverage, and strong associations with other warning systems, the data from poison centers can be used to monitor prescription drug abuse and misuse in the U.S.
Table 4: Annual reported toxic exposure cases to HCPs and oxycodone products. Rates of toxic exposure cases are calculated using extended units dispensed, extended units/mg/unit, and kilograms (kg) \(^\#\) distributed as denominators.

<table>
<thead>
<tr>
<th></th>
<th>HCPs(^\delta)</th>
<th>Oxycodone products(^\delta)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Cases/million extended units(^\Omega)</td>
</tr>
<tr>
<td>2002</td>
<td>17,429</td>
<td>2.85</td>
</tr>
<tr>
<td>2003</td>
<td>19,578</td>
<td>2.87</td>
</tr>
<tr>
<td>2004</td>
<td>22,654</td>
<td>3.32</td>
</tr>
<tr>
<td>2005</td>
<td>22,229</td>
<td>2.88</td>
</tr>
<tr>
<td>2006*</td>
<td>22,319</td>
<td>2.76</td>
</tr>
<tr>
<td>2007</td>
<td>24,558</td>
<td>2.87</td>
</tr>
<tr>
<td>2008</td>
<td>26,306</td>
<td>3.12</td>
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<tr>
<td>2009</td>
<td>27,753</td>
<td>3.27</td>
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<tr>
<td>2010</td>
<td>28,310</td>
<td>3.27</td>
</tr>
<tr>
<td>2011</td>
<td>30,792</td>
<td>3.39</td>
</tr>
<tr>
<td>2012</td>
<td>29,391</td>
<td>3.22</td>
</tr>
</tbody>
</table>

\(^{\text{Changes in reporting were implemented in 2006.}}\)

\(^{\#}\) Data for the total kilograms of drug distributed annually were obtained from ARCOS.

\(^{\Omega}\) Data for the total extended units dispensed annually were obtained from the IMS Health’s NPA™ database.

\(^{\delta}\) In the U.S., nearly 100% of total kilogram amounts of HCPs 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 light of the above findings (by Hughes et al., 2007; Davis et al., 2013), the DEA utilized the intentional exposure calls as surrogates of abuse and misuse and evaluated the abuse and misuse potentials of HCPs and oxycodone products. The intentional exposure calls related to HCPs and oxycodone products were expressed as the percent of their corresponding total exposure calls (Table 5). The resulting percentages for both these drugs were compared to determine their relative abuse and misuse potentials. The annual intentional exposure calls involving HCPs ranged from 58 to 60% of its total exposure calls during 2001 through 2005. The corresponding numbers for oxycodone products were about 52 to 55% during the same period. The cumulative (totals from 2001 through 2005) intentional exposure calls involving HCPs and oxycodone products were 58.9 and 53.3% of their corresponding total exposure calls, respectively. These data for HCPs and oxycodone products are larger than that for all pharmaceutical substances (29.4%), all reported substances (17%), and for analgesic categories (32.5%). These data indicate that the proportion (i.e. rates expressed as percent of all types of exposure calls) of intentional exposures (considered as surrogate measure of abuse and misuse) relative to the total exposures of all reasons for HCPs are slightly higher than that of oxycodone products and both these drug products have rates higher than that of the above-mentioned other categories of substances.

Table 5. Annual reported intentional toxic exposure cases relative to total toxic exposures cases involving HCPs and oxycodone products from 2001 through 2005 (NPDS)

<table>
<thead>
<tr>
<th></th>
<th>HCPs</th>
<th>Oxycodone products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total exposures</td>
<td>Intentional exposures</td>
</tr>
<tr>
<td>2001</td>
<td>15,191</td>
<td>8836 (58.2%)</td>
</tr>
<tr>
<td>2002</td>
<td>17,429</td>
<td>10301 (59.1%)</td>
</tr>
<tr>
<td>2003</td>
<td>19,578</td>
<td>11310 (57.8%)</td>
</tr>
<tr>
<td>2004</td>
<td>22,654</td>
<td>13369 (59.0%)</td>
</tr>
<tr>
<td>2005</td>
<td>22,229</td>
<td>13372 (60.2%)</td>
</tr>
<tr>
<td>Totals (2001-2005)</td>
<td>97,081</td>
<td>57,188 (58.9%)</td>
</tr>
</tbody>
</table>

Since 2006, NPDS has published information regarding single substance toxic exposures. No drugs other than the drug in question are mentioned in the single substance toxic exposures. Thus these single substance exposure data lack any possible complicating influence that may result from simultaneous exposure with other substances. The above mentioned analysis as applied to these single substance exposure data (from 2006 through 2012) for HCPs and oxycodone products resulted in findings similar to those obtained using all toxic exposures for these drugs (Table 6). The annual intentional single substance exposure calls involving HCPs ranged from 43.5 to 46.7% of its total single substance exposure calls during 2006 through 2012. The corresponding numbers for oxycodone products were about 37.8 to 43.8% during the same period. The cumulative (totals from 2006 through 2012) intentional single substance exposure calls involving HCPs and oxycodone products were 45.4 and 40.5% of their corresponding total
single substance exposure calls, respectively. These data for HCPs and oxycodone products are larger than that for all pharmaceutical substances (17%), all reported substances (9.5%), and analgesic categories (26.4%). These data indicate that the proportion (i.e. rates expressed as percent of all types of exposure calls) of intentional single substance exposures (considered as surrogate measure of abuse and misuse) relative to the total single substance exposures of all reasons for HCPs are slightly higher than that of oxycodone products and both these drug products have rates higher than that of the above-mentioned categories of substances. These findings on intentional single substance exposure data from 2006 through 2012 are similar to those mentioned above for total exposure data from 2001 through 2005.

Table 6. Annual reported intentional single substance toxic exposures relative to total single substance toxic exposures involving HCPs and oxycodone products from 2006 through 2012 (NPDS)

<table>
<thead>
<tr>
<th></th>
<th>HCPs</th>
<th>Oxycodone products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total exposures</td>
<td>Intentional exposures</td>
</tr>
<tr>
<td>2006</td>
<td>10,061</td>
<td>4,379</td>
</tr>
<tr>
<td>2007</td>
<td>11,001</td>
<td>4,862</td>
</tr>
<tr>
<td>2008</td>
<td>11,834</td>
<td>5,240</td>
</tr>
<tr>
<td>2009</td>
<td>12,559</td>
<td>5,740</td>
</tr>
<tr>
<td>2010</td>
<td>12,541</td>
<td>5,855</td>
</tr>
<tr>
<td>2011</td>
<td>13,756</td>
<td>6,384</td>
</tr>
<tr>
<td>2012</td>
<td>13,046</td>
<td>6,024</td>
</tr>
<tr>
<td>Totals</td>
<td>84,798</td>
<td>38,484</td>
</tr>
</tbody>
</table>

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. HCPs had the largest 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 NPAPlus™, about 83 to 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 HCPs products followed by other oxycodone products. In contrast, when exposure rates were calculated using the number of patients prescribed as the denominator, HCPs 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 HCPs 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.

Dart et al. (2012) reviewed the poison centers data from 49 regional U.S. poison centers in 44 states, serving 312 million people and reported that poison centers received a total of 132,445 intentional exposure calls involving any prescription opioid. These investigators found that the intentional toxic exposure rates for HCPs ranged from 1.78 and 2.02 per 100,000 population while the corresponding range for oxycodone products was from 1.00 to 1.18.

Zosel et al. (2013) studied the characteristics and health effects of adolescent (age 13 to 19 years) prescription drug abuse and misuse using the data collected during 2007 through 2009 from poison centers (45 centers in 45 states encompassing 84% of all U.S. poison centers) participating in Researched Abuse Diversion and Addiction-related surveillance (RADARS) System. This study reported that a total of 16,209 adolescents had intentional exposures to prescription drugs (68% to opioids and 32% to stimulants). This study further found that the most frequently abused or misused drug was HCPs (32%) followed by amphetamines (18%), oxycodone products (15%), methylphenidate (14%) and tramadol (11%). There were 20 deaths all in opioid exposure group, and none in stimulant exposure group.

1.2.2.3. Florida Department of Law Enforcement (FDLE) medical examiners data

The HHS reviewed the medical examiners data from the FDLE22 and presented the same for HCPs and oxycodone products from 2007 through 2012. The HHS also provided data for various other opioid analgesics for the year 2012. The HHS found that FDLE reported 8,330 drug-related deaths in 2012 and majority of these decedents had more than one drug present in the system. Overall the drugs that caused most deaths included oxycodone products, alprazolam, ethanol, cocaine, methadone, morphine diazepam and HCPs. The HHS states that a variety of factors such as state efforts to respond to the emergence of “pill mills” by legislation restricting a prescriber’s ability to dispense oxycodone products and other controlled substances from a pain clinic prevent the analysis of these data to examine the trends over time. The HHS summarized that HCPs are linked to a substantial number of overdose deaths each year in Florida and these data also support its conclusion that HCPs are contributing to substantial numbers of deaths each year in the U.S.

The DEA further finds from ARCOS data that from 2002 through 2005, the amount of hydrocodone distributed annually in Florida was approximately same as the amount of oxycodone distributed (Table 7). Similarly, HCPs-related deaths are approximately the same as the oxycodone products-related deaths during this period. Although there were gradual increases in the distribution of both HCPs and oxycodone products, the maximal increase for HCPs (80%) was less than the maximal increase for oxycodone products (571%) when compared to corresponding data for 2002. Mortality data also showed similar trends. The maximal increase for HCPs (72%) related deaths was less than the maximal increase for oxycodone products (405%) when compared to corresponding data for 2002. Total annual prescriptions dispensed for HCPs exceeded those for oxycodone products from 2005 through 2012, while the total dosage

22 FDLE reports all drug-related deaths (whether implicated as the cause of death or mentioned as merely present) from all counties in the state of Florida, annually, for the twelve month period and the six-month interim.
units distributed did not show consistent differences between these two products. The average milligram amount for each unit of oxycodone products distributed is higher than that of HCPs from 2006 through 2012 (Table 7).

Table 7. Annual drug related deaths, drug quantities (kilograms) and dosage units (“extended units”) distributed (ARCOSΨ) and total prescriptions (NPAPlus™) dispensed for HCPs and oxycodone products in Florida from 2002 through 2012§

<table>
<thead>
<tr>
<th>Year</th>
<th>HCPs</th>
<th>Oxycodone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>Drug amount distributed (kg in salt form)</td>
</tr>
<tr>
<td>2002</td>
<td>554</td>
<td>2,101</td>
</tr>
<tr>
<td>2003</td>
<td>572</td>
<td>2,629</td>
</tr>
<tr>
<td>2004</td>
<td>632</td>
<td>3,066</td>
</tr>
<tr>
<td>2005</td>
<td>648</td>
<td>3,253</td>
</tr>
<tr>
<td>2006</td>
<td>731</td>
<td>3,785</td>
</tr>
<tr>
<td>2007</td>
<td>807</td>
<td>3,576</td>
</tr>
<tr>
<td>2008</td>
<td>870</td>
<td>3,255</td>
</tr>
<tr>
<td>2009</td>
<td>865</td>
<td>3,324</td>
</tr>
<tr>
<td>2010</td>
<td>958</td>
<td>3,265</td>
</tr>
<tr>
<td>2011</td>
<td>877</td>
<td>3,339</td>
</tr>
<tr>
<td>2012</td>
<td>777</td>
<td>3,105</td>
</tr>
</tbody>
</table>

ΨThe vast majority of oxycodone products are formulated in the hydrochloride salt form while HCPs 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.

The annual rates of deaths, calculated as deaths per million extended units distributed, related to HCPs are lower (from 1.5 to 1.9-fold) as compared to the corresponding rates of deaths for oxycodone products from 2006 through 2012 (Table 8). However, the annual rates of deaths, calculated as deaths per kilogram of HCPs distributed were similar or slightly higher than that of oxycodone products. As mentioned earlier, ideal comparison is between HCPs and oxycodone combination products, but not alloxycodone products. However, due to lack of formulation-specific mortality data, such analyses are not possible.
Table 8: Annual rates of drug-related deaths in Florida for HCPs and oxycodone products. Rates are calculated using dosage units and kilograms (kg) of drug distributed as denominators.

<table>
<thead>
<tr>
<th></th>
<th>HCPs</th>
<th></th>
<th>Oxycodone products</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths/ million dosage units</td>
<td>Deaths/kg</td>
<td>Deaths/ million dosage units</td>
<td>Deaths/kg</td>
</tr>
<tr>
<td>2006</td>
<td>1.68</td>
<td>0.19</td>
<td>3.23</td>
<td>0.21</td>
</tr>
<tr>
<td>2007</td>
<td>1.88</td>
<td>0.23</td>
<td>3.15</td>
<td>0.19</td>
</tr>
<tr>
<td>2008</td>
<td>2.19</td>
<td>0.27</td>
<td>3.65</td>
<td>0.20</td>
</tr>
<tr>
<td>2009</td>
<td>2.12</td>
<td>0.26</td>
<td>3.71</td>
<td>0.19</td>
</tr>
<tr>
<td>2010</td>
<td>2.39</td>
<td>0.29</td>
<td>3.66</td>
<td>0.17</td>
</tr>
<tr>
<td>2011</td>
<td>2.12</td>
<td>0.26</td>
<td>4.04</td>
<td>0.21</td>
</tr>
<tr>
<td>2012</td>
<td>2.03</td>
<td>0.25</td>
<td>3.8</td>
<td>0.24</td>
</tr>
</tbody>
</table>

# Data for the total kilograms and dosage units of drug distributed annually were obtained from ARCOS.

In summary the above mentioned analysis of drug-related mortality data in Florida suggest that both HCPs and oxycodone products are associated with large numbers of deaths and have large adverse impact on public health in this state. The relative potential to cause adverse health risk per kilogram of HCPs distributed is similar or slightly higher than that of oxycodone products in Florida.

1.2.3. Criterion 2: There is a significant diversion of drug or other substance from legitimate drug channels.

As discussed below, there is a significant diversion of HCPs from legitimate drug channels.

1.2.3.1. Forensic laboratory data

The data from the NFLIS and the STRIDE are presented in Table 9. 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.

According to NFLIS, from 2002 through 2008, HCPs cases and exhibits exceeded that of oxycodone products, while in 2009 these were approximately similar. However, in recent years
(from 2010 through 2012) oxycodone products cases and exhibits exceeded that of HCPs (Table 9). According NFLIS annual reports, both HCPs and oxycodone products have been consistently mentioned as among the top 10 most frequently encountered drugs over the past ten years and these are the leading diverted controlled pharmaceuticals among opioid analgesics drugs.

Table 9. Total cases and drug exhibits reported in NFLIS (Data for 2002 through 2003 were retrieved on March 14, 2008 and for 2004 through 2012 were retrieved on January 7, 2014) and STRIDE (data for 1996 through 2003 were retrieved on March 21, 2008 and for 2004 through 2012 were retrieved on January 7, 2014)§

<table>
<thead>
<tr>
<th>Year</th>
<th>HCPs</th>
<th>Oxycodone products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NFLIS</td>
<td>STRIDE</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>Exhibits</td>
</tr>
<tr>
<td>1996</td>
<td>56</td>
<td>139</td>
</tr>
<tr>
<td>1997</td>
<td>56</td>
<td>187</td>
</tr>
<tr>
<td>1998</td>
<td>59</td>
<td>103</td>
</tr>
<tr>
<td>1999</td>
<td>98</td>
<td>235</td>
</tr>
<tr>
<td>2000</td>
<td>105</td>
<td>259</td>
</tr>
<tr>
<td>2001</td>
<td>134</td>
<td>315</td>
</tr>
<tr>
<td>2002</td>
<td>8934</td>
<td>10174</td>
</tr>
<tr>
<td>2003</td>
<td>11429</td>
<td>13179</td>
</tr>
<tr>
<td>2004</td>
<td>16,097</td>
<td>17,769</td>
</tr>
<tr>
<td>2005</td>
<td>20,776</td>
<td>22,939</td>
</tr>
<tr>
<td>2006</td>
<td>24,543</td>
<td>27,270</td>
</tr>
<tr>
<td>2007</td>
<td>30,168</td>
<td>33,710</td>
</tr>
<tr>
<td>2008</td>
<td>33,396</td>
<td>37,943</td>
</tr>
<tr>
<td>2009</td>
<td>37,627</td>
<td>43,432</td>
</tr>
<tr>
<td>2010</td>
<td>38,992</td>
<td>45,082</td>
</tr>
<tr>
<td>2011</td>
<td>36,970</td>
<td>43,237</td>
</tr>
<tr>
<td>2012</td>
<td>34,585</td>
<td>40,249</td>
</tr>
</tbody>
</table>

§In the U.S., nearly 100% (of total kilogram amounts distributed) of HCPs was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone products were marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

According to STRIDE, from 1996 through 2000, cases and exhibits involving HCPs exceeded those of oxycodone products (Table 9). However in recent years (especially from 2007) cases and exhibits involving oxycodone products exceeded those of HCPs. From 2001 through 2006 no consistent pattern of differences were found. Similar to NFLIS, STRIDE has also consistently reported that HCPs and oxycodone products are the leading diverted controlled pharmaceuticals among the opioid analgesics drugs. Average number of solid dosage units (comprising of tablets and capsules) per each case was 2.3-fold larger for HCPs than for oxycodone products (Table 10).
Table 10. Cumulative total amounts of drug exhibits for HCPs and oxycodone products reported by STRIDE from 1996 through 2012 (data retrieved on January 30, 2014) §

<table>
<thead>
<tr>
<th>Measure</th>
<th>HCPs</th>
<th>Oxycodone products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Solid Dosage Units (Tablets or Capsules)</td>
<td>Powder (Grams)</td>
</tr>
<tr>
<td>Totals</td>
<td>2,55,109</td>
<td>20,364</td>
</tr>
<tr>
<td>Average/Case*</td>
<td>890</td>
<td>7.1</td>
</tr>
</tbody>
</table>

* Averages per case basis was calculated by using the total number of cases recorded.

§ In the U.S., nearly 100% (of total kilogram amounts distributed) of HCPs was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone products were 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 diversion of oxycodone products, calculated as annual forensic drug exhibits (NFLIS + STRIDE) per million extended units dispensed are higher (a range of 2.1 to 3.3-fold) as compared to the corresponding rates for HCPs from 2002 through 2012 (Table 11). However, when the differences in drug amounts in extended units of HCPs versus oxycodone products were taken into account (by dividing the above rates with average milligram drug amounts per extended unit data as denominator), these differences in rates between HCPs and oxycodone products were reduced to 1.2 to 1.7-fold (Table 11). Contrary to the rates obtained using extended units dispensed as the denominator, the rates of diversion per kilogram of HCPs distributed were largely similar to (2002-2004, 2009), slightly higher (2005-2008) or slightly lower (2010-2012) than that of oxycodone products. As mentioned earlier, ideal comparison is between HCPs and oxycodone combination products, but not all oxycodone products. However, due to lack of formulation-specific data, such analyses are not possible.

The above analysis using forensic drug cases as the numerator produced essentially similar results as seen with forensic drug exhibits as the numerator (Table 12).
Table 11: Total forensic drug exhibits reported in NFLIS\(^8\) and STRIDE databases\(^8\). Rates of diversion are calculated using forensic drug exhibits as the numerator and extended units dispensed, extended units/milligram/unit, and kilograms\(^#\) distributed as denominators.

<table>
<thead>
<tr>
<th>Year</th>
<th>Exhibits (NFLIS+STRIDE)</th>
<th>Exhibits/million extended units</th>
<th>Exhibits/million extended units/milligram/unit</th>
<th>Exhibits/kilograms(^#)</th>
<th>Exhibits (NFLIS+STRIDE)</th>
<th>Exhibits/million extended units</th>
<th>Exhibits/million extended units/milligram/unit</th>
<th>Exhibits/kilograms(^#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>10,511</td>
<td>1.72</td>
<td>0.25</td>
<td>0.34</td>
<td>9,464</td>
<td>5.62</td>
<td>0.42</td>
<td>0.38</td>
</tr>
<tr>
<td>2003</td>
<td>13,699</td>
<td>2.01</td>
<td>0.28</td>
<td>0.37</td>
<td>11,311</td>
<td>5.78</td>
<td>0.43</td>
<td>0.38</td>
</tr>
<tr>
<td>2004</td>
<td>18,303</td>
<td>2.68</td>
<td>0.37</td>
<td>0.46</td>
<td>15,519</td>
<td>7.26</td>
<td>0.55</td>
<td>0.48</td>
</tr>
<tr>
<td>2005</td>
<td>23,537</td>
<td>3.05</td>
<td>0.42</td>
<td>0.56</td>
<td>17,057</td>
<td>7.14</td>
<td>0.54</td>
<td>0.50</td>
</tr>
<tr>
<td>2006</td>
<td>27,929</td>
<td>3.45</td>
<td>0.47</td>
<td>0.57</td>
<td>21,155</td>
<td>7.74</td>
<td>0.58</td>
<td>0.51</td>
</tr>
<tr>
<td>2007</td>
<td>34,451</td>
<td>4.02</td>
<td>0.55</td>
<td>0.64</td>
<td>26,479</td>
<td>8.61</td>
<td>0.63</td>
<td>0.55</td>
</tr>
<tr>
<td>2008</td>
<td>38,424</td>
<td>4.56</td>
<td>0.62</td>
<td>0.65</td>
<td>34,658</td>
<td>10.01</td>
<td>0.72</td>
<td>0.63</td>
</tr>
<tr>
<td>2009</td>
<td>44,083</td>
<td>5.20</td>
<td>0.69</td>
<td>0.71</td>
<td>46,597</td>
<td>12.40</td>
<td>0.88</td>
<td>0.75</td>
</tr>
<tr>
<td>2010</td>
<td>45,707</td>
<td>5.28</td>
<td>0.70</td>
<td>0.71</td>
<td>60,259</td>
<td>14.04</td>
<td>0.97</td>
<td>0.85</td>
</tr>
<tr>
<td>2011</td>
<td>43,931</td>
<td>4.83</td>
<td>0.64</td>
<td>0.63</td>
<td>58,396</td>
<td>12.74</td>
<td>0.91</td>
<td>0.82</td>
</tr>
<tr>
<td>2012</td>
<td>40,774</td>
<td>4.46</td>
<td>0.58</td>
<td>0.60</td>
<td>52,846</td>
<td>11.52</td>
<td>0.85</td>
<td>0.78</td>
</tr>
</tbody>
</table>

\(^8\)NFLIS data from 1996 through 2003 were retrieved on March 14, 2008 and the data from 2004 through 2012 were retrieved on January 7, 2014. STRIDE data from 1996 through 2003 were retrieved on March 21, 2008 and the data from 2004 through 2012 were retrieved on January 7, 2014.

\(^#\)Data for the total kilograms of drug distributed annually were obtained from ARCOS.

\(^\text{\dag}\)Data for the total extended units dispensed annually were obtained from the IMS Health’s NPA\(^\text{TM}\).
Table 12: Total forensic drug cases reported in NFLIS$^§$ and STRIDE$^§$ databases. Rates of diversion are calculated using forensic drug cases as the numerator and extended units dispensed, extended units/milligram/unit, and kilograms$^#$ distributed as denominators.

<table>
<thead>
<tr>
<th>Year</th>
<th>HCPs Cases (NFLIS+STRIDE)</th>
<th>HCPs Cases/million extended units$^a$</th>
<th>HCPs Cases/million extended units/milligram/unit</th>
<th>HCPs Cases/kg$^#$</th>
<th>Oxycodone Cases (NFLIS+STRIDE)</th>
<th>Oxycodone Cases/million extended units$^a$</th>
<th>Oxycodone Cases/million extended units/milligram/unit</th>
<th>Oxycodone Cases/kg$^#$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>9,106</td>
<td>1.49</td>
<td>0.21</td>
<td>0.30</td>
<td>7,993</td>
<td>4.75</td>
<td>0.36</td>
<td>0.32</td>
</tr>
<tr>
<td>2003</td>
<td>11,617</td>
<td>1.70</td>
<td>0.24</td>
<td>0.32</td>
<td>9,431</td>
<td>4.82</td>
<td>0.36</td>
<td>0.32</td>
</tr>
<tr>
<td>2004</td>
<td>16,299</td>
<td>2.39</td>
<td>0.33</td>
<td>0.41</td>
<td>13,342</td>
<td>6.25</td>
<td>0.47</td>
<td>0.41</td>
</tr>
<tr>
<td>2005</td>
<td>21,019</td>
<td>2.72</td>
<td>0.38</td>
<td>0.50</td>
<td>14,417</td>
<td>6.03</td>
<td>0.46</td>
<td>0.42</td>
</tr>
<tr>
<td>2006</td>
<td>24,798</td>
<td>3.06</td>
<td>0.42</td>
<td>0.51</td>
<td>17,733</td>
<td>6.49</td>
<td>0.48</td>
<td>0.43</td>
</tr>
<tr>
<td>2007</td>
<td>30,411</td>
<td>3.55</td>
<td>0.48</td>
<td>0.56</td>
<td>22,160</td>
<td>7.21</td>
<td>0.52</td>
<td>0.46</td>
</tr>
<tr>
<td>2008</td>
<td>33,611</td>
<td>3.99</td>
<td>0.54</td>
<td>0.57</td>
<td>28,343</td>
<td>8.19</td>
<td>0.59</td>
<td>0.52</td>
</tr>
<tr>
<td>2009</td>
<td>37,894</td>
<td>4.47</td>
<td>0.60</td>
<td>0.61</td>
<td>37,680</td>
<td>10.03</td>
<td>0.71</td>
<td>0.61</td>
</tr>
<tr>
<td>2010</td>
<td>39,261</td>
<td>4.53</td>
<td>0.60</td>
<td>0.61</td>
<td>47,238</td>
<td>11.01</td>
<td>0.76</td>
<td>0.66</td>
</tr>
<tr>
<td>2011</td>
<td>37,314</td>
<td>4.10</td>
<td>0.54</td>
<td>0.53</td>
<td>45,908</td>
<td>10.02</td>
<td>0.71</td>
<td>0.65</td>
</tr>
<tr>
<td>2012</td>
<td>34,832</td>
<td>3.81</td>
<td>0.49</td>
<td>0.51</td>
<td>41,915</td>
<td>9.14</td>
<td>0.67</td>
<td>0.62</td>
</tr>
</tbody>
</table>

$^§$NFLIS data from 1996 through 2003 were retrieved on March 14, 2008 and the data from 2004 through 2012 were retrieved on January 7, 2014. STRIDE data from 1996 through 2003 were retrieved on March 21, 2008 and the data from 2004 through 2012 were retrieved on January 7, 2014.

$^a$Data for the total extended units dispensed annually were obtained from the IMS Health’s NPA™ database.

In summary, forensic laboratory data (NFLIS and STRIDE) indicate that HCPs and oxycodone products are widely diverted. These are the leading diverted controlled pharmaceuticals among opioid analgesic drugs.
1.2.3.2. **Diversion from Internet pharmacies**

An investigation by the General Accounting Office in 2004 indicated the availability of HCPs products through Internet without a prescription and the GAO reached the following conclusion at that time (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 in the past revealed that the nonmedical use of controlled pharmaceuticals, specifically HCPs, 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 collaborated, 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 13 provides ARCOS data for the distribution of controlled opioid analgesics to 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 and as morphine equivalent amounts.

The above mentioned 71 pharmacies ordered a cumulative total of 1,041.3 kilograms of HCPs from 2005 through 2007 that are markedly larger than the corresponding average amounts ordered by all pharmacies in the U.S (Table 14). Average amounts of HCPs 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 HCPs. 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 HCPs ordered.
Table 13. Opioid analgesic drug sales (in grams) to 71 pharmacies (identified by DEA) suspected to have filled illegal Internet prescriptions (ARCOS)*

<table>
<thead>
<tr>
<th>Narcotics</th>
<th>2005 Amounts</th>
<th>Amounts in Morphine equivalents</th>
<th>2006 Amounts</th>
<th>Amounts in Morphine equivalents</th>
<th>2007 Amounts</th>
<th>Amounts in Morphine equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCPs</td>
<td>343,732 (74.0%)</td>
<td>687,464 (77.0%)</td>
<td>510,932 (77.0%)</td>
<td>1,021,864 (80.7%)</td>
<td>186,645 (54.0%)</td>
<td>373,290 (56.1%)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>51,777 (11.2%)</td>
<td>103,554 (11.6%)</td>
<td>66,938 (10.0%)</td>
<td>133,876 (10.6%)</td>
<td>96,574 (28.0%)</td>
<td>193,148 (29.0%)</td>
</tr>
<tr>
<td>Codeine</td>
<td>30,209 (6.5%)</td>
<td>11,479 (1.3%)</td>
<td>38,041 (6.0%)</td>
<td>14,456 (1.1%)</td>
<td>23,190 (6.7%)</td>
<td>8,812 (1.3%)</td>
</tr>
<tr>
<td>Morphine</td>
<td>13,924 (3.0%)</td>
<td>13,924 (1.6%)</td>
<td>16,663 (2.5%)</td>
<td>16,663 (1.3%)</td>
<td>14,574 (4.2%)</td>
<td>14,574 (2.2%)</td>
</tr>
<tr>
<td>Methadone</td>
<td>11,370 (2.5%)</td>
<td>34,110 (3.8%)</td>
<td>11,834 (1.8%)</td>
<td>35,502 (2.8%)</td>
<td>13,981 (4.0%)</td>
<td>41,943 (6.3%)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>893 (&lt;1.0% )</td>
<td>22,325 (2.5%)</td>
<td>1,021 (&lt;1.0% )</td>
<td>25,525 (2.0%)</td>
<td>519 (&lt;1.0% )</td>
<td>12,975 (2.0%)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>357 (&lt;1.0% )</td>
<td>8,925 (1.0%)</td>
<td>362 (&lt;1.0% )</td>
<td>9,050 (&lt;1.0% )</td>
<td>339 (&lt;1.0% )</td>
<td>8,475 (1.3%)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>884 (&lt;1.0% )</td>
<td>7,072 (0.8%)</td>
<td>965 (&lt;1.0% )</td>
<td>7,720 (&lt;0.6% )</td>
<td>931 (&lt;1.0% )</td>
<td>7,448 (1.1%)</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>-</td>
<td>54 (&lt;1.0% )</td>
<td>540 (&lt;1.0% )</td>
<td>346 (&lt;1.0% )</td>
<td>3,460 (&lt;1.0% )</td>
<td>696 (&lt;1.0% )</td>
</tr>
<tr>
<td>Meperidine</td>
<td>1,802 (&lt;1.0% )</td>
<td>360 (&lt;1.0% )</td>
<td>1,922 (&lt;1.0% )</td>
<td>384 (&lt;1.0% )</td>
<td>3,481 (1.0% )</td>
<td>696 (&lt;1.0% )</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>28.4 (&lt;1.0% )</td>
<td>28.4 (&lt;1.0% )</td>
<td>13 (&lt;1.0% )</td>
<td>13 (&lt;1.0% )</td>
<td>34 (&lt;1.0% )</td>
<td>34 (&lt;1.0% )</td>
</tr>
<tr>
<td>Opium Powder</td>
<td>18 (&lt;1.0% )</td>
<td>8 (&lt;1.0% )</td>
<td>8 (&lt;1.0% )</td>
<td>6 (&lt;1.0% )</td>
<td>6 (&lt;1.0% )</td>
<td>6 (&lt;1.0% )</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>1.1 (&lt;1.0% )</td>
<td>16.5 (&lt;1.0% )</td>
<td>1.2 (&lt;1.0% )</td>
<td>18 (&lt;1.0% )</td>
<td>1.6 (&lt;1.0% )</td>
<td>24 (&lt;1.0% )</td>
</tr>
</tbody>
</table>

*Data expressed in grams for base forms of these drugs. Numerals in parentheses indicate amount as the percent of all controlled substances.

*Morphine 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 equi-analgesic doses mentioned by Gutstein and Akil (2006). Dihydrocodeine was considered equipotent to morphine based on oral dose formulations available in the market.
Table 14. 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)

<table>
<thead>
<tr>
<th>Drug</th>
<th>2005 U.S. Pharmacy Average</th>
<th>Rogue Internet Pharmacy Average</th>
<th>2006 U.S. Pharmacy Average</th>
<th>Rogue Internet Pharmacy Average</th>
<th>2007 U.S. Pharmacy Average</th>
<th>Rogue Internet Pharmacy Average</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grams</td>
<td>% of U.S. Pharmacy Average</td>
<td>Grams</td>
<td>% of U.S. Pharmacy Average</td>
<td>Grams</td>
<td>% of U.S. Pharmacy Average</td>
</tr>
<tr>
<td>HCPs</td>
<td>398.82</td>
<td>1,214%</td>
<td>454.7</td>
<td>1,583%</td>
<td>496.8</td>
<td>529%</td>
</tr>
<tr>
<td>Oxycodone products</td>
<td>488.55</td>
<td>149%</td>
<td>585.6</td>
<td>161%</td>
<td>673.0</td>
<td>202%</td>
</tr>
<tr>
<td>Codeine</td>
<td>284.26</td>
<td>150%</td>
<td>277.6</td>
<td>193%</td>
<td>271.3</td>
<td>120%</td>
</tr>
<tr>
<td>Morphine</td>
<td>222.83</td>
<td>88%</td>
<td>259.1</td>
<td>91%</td>
<td>274.3</td>
<td>75%</td>
</tr>
<tr>
<td>Methadone</td>
<td>100.28</td>
<td>160%</td>
<td>119.8</td>
<td>139%</td>
<td>126.8</td>
<td>155%</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>6.84</td>
<td>184%</td>
<td>9.4</td>
<td>152%</td>
<td>12.6</td>
<td>58%</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>6.05</td>
<td>83%</td>
<td>6.6</td>
<td>77%</td>
<td>6.9</td>
<td>69%</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>13.55</td>
<td>92%</td>
<td>14.8</td>
<td>92%</td>
<td>15.9</td>
<td>82%</td>
</tr>
</tbody>
</table>

Data expressed are gram amounts of drug in base form.

On January 22, 2007, the DEA launched “Operation Lightning Strike,” an initiative that targeted DEA registered pharmacies that allegedly were filling illegal controlled substance prescriptions from customers over numerous websites. By February 21, 2007, the DEA had suspended all six targeted pharmacies and two additional pharmacies that were filling illegal Internet prescriptions for controlled substances. The DEA removed 907,238 dosage units of HCPs and bulk hydrocodone (equivalent to 600,000 ten-milligram dosage units). U.S. pharmacies on average purchase less than 8,000 dosage units of HCPs per month. Each suspended pharmacy possessed more than 21,000 dosage units of HCPs. 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 HCPs in 2006, the vast majority of which were used to fill orders placed by customers illegally over the Internet.

1.2.4. Criterion 3: 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.

Drug abuse data from national surveys indicate that individuals are taking HCPs on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs.

1.2.4.1. 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. NSDUH reports yearly national and state level estimates of alcohol, tobacco, illicit drug and nonmedical use of prescription drugs. The HHS compared the substance use prevalence estimates by lifetime (i.e., ever used) for HCPs and oxycodone products for years 2004 and 2012. The “Lifetime prevalence” is a cumulative indicator of the number of people who have ever tried a given drug.
The HHS mentioned that in 2012, about 54 million U.S. population age 12 or older used prescription-type psychotherapeutic drugs nonmedically at least once in their lifetime (lifetime use) and these numbers are significantly higher than the corresponding numbers in 2004. Of these 54 million U.S. population, 37 million used pain relievers; 23.6 million used tranquilizers, 21.5 million used stimulants, and approximately 7.9 million used sedatives. With the exception of stimulants, these 2012 estimates are significantly higher than the corresponding estimates for 2011. Of the 37 million U.S. population who used pain relievers nonmedically in their lifetime, over 25.6 million (representing 9.9% of the U.S. population age 12 years or older) reported lifetime nonmedical use of HCPs, while over 16 million (6.2% of U.S. population age 12 years or older) reported nonmedical use of oxycodone products.

The HHS stated that the overall annual availability of HCPs was three to four-fold greater than that of oxycodone products, based on the number of prescriptions dispensed in 2011. When adjusted for these differences in availability, the numbers of lifetime nonmedical use of HCPs are approximately half of those of oxycodone products. The HHS summarized that the numbers for lifetime nonmedical use of HCPs is higher than those for oxycodone products. The numbers for HCPs in 2012 are substantially higher than those in 2004. According to the HHS, these data support the conclusion that HCPs are abused more than oxycodone products in this population, although its rates of abuse are lower than that of oxycodone products and these data point to the large increasing numbers of individuals in the U.S. who have used HCPs and oxycodone products for nonmedical purposes.

The DEA further notes that according to a report by NSDUH (2007), the combined data from 2002 through 2005 indicate that 57.7% of persons who first used pain relievers nonmedically in the past year used HCPs products whereas 21.7% used oxycodone products. Similarly, HHS’s earlier scientific and medical evaluation submitted to DEA in 2008 provided NSDUH data regarding past year initiates of HCPs and oxycodone products for the years 2002 through 2005 (Table 15). These data show that past year initiates (defined as persons who used the substance for the first time in the 12 months prior to date of interview) of HCPs were about 2.2- to 2.9-fold higher than those of oxycodone products. For example, in 2005, about 1.3 million individuals (12 years or older) were past year initiates for HCPs. The corresponding number for oxycodone products was 0.45 million.

The rates of past year initiates, calculated as the number of past year initiates per million extended units, for HCPs are slightly lower (about 1.1 to 1.4-fold in 2002, 2003 and 2005) as compared to the corresponding rates for oxycodone combination products (Table 15). However, when the differences in drug amounts in extended units of HCPs versus oxycodone products were taken into account (by dividing the above rates with average milligram drug amounts per extended unit data as denominator), these differences in rates between HCPs and oxycodone products were reversed and HCPs had higher rates (1.3 to 1.6-fold) than oxycodone products. Similarly, contrary to the rates obtained using extended units dispensed as the denominator, the rates of past year initiates per kilogram of HCPs distributed were higher (1.8 to 2.3-fold) than that of oxycodone products.
Table 15. Past year initiates of nonmedical use of HCPs and oxycodone products

<table>
<thead>
<tr>
<th>Year</th>
<th>Past year initiates (thousands)</th>
<th>HCPs</th>
<th>Oxycodone products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Past year initiates/million extended units</td>
<td>221</td>
<td>282</td>
</tr>
<tr>
<td></td>
<td>Past year initiates/million extended units/milligram/unit</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Past year initiates/kilogram#</td>
<td>44</td>
<td>19</td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Past year initiates/million extended units</td>
<td>206</td>
<td>257</td>
</tr>
<tr>
<td></td>
<td>Past year initiates/million extended units/milligram/unit</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Past year initiates/kilogram#</td>
<td>38</td>
<td>17</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Past year initiates/million extended units</td>
<td>198</td>
<td>285</td>
</tr>
<tr>
<td></td>
<td>Past year initiates/million extended units/milligram/unit</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Past year initiates/kilogram#</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Past year initiates/million extended units</td>
<td>170</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td>Past year initiates/million extended units/milligram/unit</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Past year initiates/kilogram#</td>
<td>31</td>
<td>13</td>
</tr>
</tbody>
</table>

1Includes Vicodin®, Lortab®, or Lorcet®, and generic HCP and other pain relievers containing hydrocodone that respondents specified.
2Includes Percocet®, Percodan®, or Tylox® and OxyContin® and other pain relievers containing oxycodone that respondents specified.
3Data for the total kilograms of drug distributed annually were obtained from ARCOS.
4Data for the total extended units dispensed annually were obtained from the IMS Health’s NPA™ database.
5In the U.S., nearly 100% (of total kilogram amounts distributed) of HCPs was marketed as combination products.
that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone products were marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).

The NSDUH data provided by the HHS in its 2008 scientific and medical evaluation also indicate that the percentages of lifetime nonmedical users of HCPs reporting past year use of any pain relievers is similar to that of oxycodone products for the years 2002 through 2005. The 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 HCPs 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 nonmedical purpose with in the past year. These data are shown in Table 16. Percentages of lifetime users of specific pain relievers who used any pain reliever in the past year are shown in parentheses in Table 16.

The data indicate that considerable numbers of lifetime users of pain relievers have used these drugs for nonmedical 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 HCPs were 5.78 million and 9.04 million, 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 (Table 16). Percentages of lifetime users of HCPs (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® 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 less than those of the lifetime users of HCPs and all oxycodone products.
Table 16. Lifetime nonmedical users of any pain relievers, HCPs, 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 nonmedical purpose in the past year§

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Numbers in Thousands (Percentages)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2002</td>
</tr>
<tr>
<td>Any Pain Reliever</td>
<td>29,611</td>
</tr>
<tr>
<td>HCPs§</td>
<td>13,952</td>
</tr>
<tr>
<td>OxyContin®</td>
<td>1,294</td>
</tr>
<tr>
<td>Oxycodone Products Other than OxyContin®</td>
<td>10,151</td>
</tr>
<tr>
<td>Any Past Year Pain Reliever Use Among Lifetime Users of Any Pain Reliever</td>
<td>10,992</td>
</tr>
<tr>
<td>HCPs§</td>
<td>6,782</td>
</tr>
<tr>
<td>OxyContin®</td>
<td>1,366</td>
</tr>
<tr>
<td>Oxycodone Products Other than OxyContin®</td>
<td>4,286</td>
</tr>
<tr>
<td>Oxycodone Products Other than OxyContin®</td>
<td>2,920</td>
</tr>
</tbody>
</table>

*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.

1Includes other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category.

2Includes Vicodin®, Lortab®, or Lorcet®, and hydrocodone.

3Includes Percocet®, Percodan® or Tylox®, and OxyContin®.

§In the U.S., nearly 100% (of total kilogram amounts distributed) of HCPs was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone products were 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 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), HCPs (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 slightly less (1.2 to 1.4-fold) than that of the lifetime users of HCPs.

These data indicate that the lifetime users of HCPs have higher propensity than that of lifetime users of oxycodone immediate release products (single-entity and combination products combined) to have used for nonmedical 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, NSDUH data from 2002 through 2005 show that past year initiates of HCPs were about 2.2- to 2.9-fold higher than those of oxycodone products. The past year initiates per million extended units for HCPs are slightly lower (for 2002, 2003, and 2005) as compared to the corresponding rates for oxycodone products (Table 15). However, when the differences in drug amounts in extended units of HCPs versus oxycodone products were taken into account, these differences in rates between HCPs and oxycodone products were reversed and HCPs had higher rates than oxycodone products. Similarly, contrary to the rates obtained using extended units dispensed as the denominator, the past year initiates per kilogram HCPs distributed were higher than that of oxycodone products. The lifetime users of HCPs have higher propensity than that of lifetime users of oxycodone immediate release products (single-entity and combination products combined) to have used for nonmedical purpose any pain relievers in the past year. The NSDUH data collectively indicate that nonmedical use of both HCPs and oxycodone products is large suggesting these products have high abuse potential.

1.2.4.2. Monitoring the Future (MTF)

Monitoring the Future (MTF) is a questionnaire based survey of drug use among secondary 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 prevalence of abuse of HCPs and oxycodone products among students could not be computed. However, MTF did provide product-specific information for two opioid analgesic products, namely Vicodin®, a HCP, and OxyContin®, an oxycodone extended release single-entity product. The HHS reviewed these product-specific data and found that overall the annual prevalence of nonmedical use of Vicodin® was higher than that of OxyContin® among high school students. According to the HHS, in 2012 the annual prevalences of nonmedical use of OxyContin® were 1.6%, 3.0%, and 4.3% among 8th, 10th, and 12th graders, respectively. The prevalence of Vicodin® was higher among the older students. The corresponding prevalences of nonmedical use of Vicodin® were 1.3%, 4.4%, and 7.5%, respectively.

DEA further notes that from 2002 through 2011, the annual prevalence of the nonmedical use of Vicodin® (ranges: 2.1 – 3.0% of 8th graders; 5.9 – 8.1% of 10th graders; 8.1% – 10.5% of 12th graders) was higher than that of OxyContin® (ranges: 1.3 – 2.6% of 8th graders; 3.0 – 5.1% of 10th graders; 4.0% – 5.5% of 12th graders). In 2011, the annual prevalences for Vicodin® among 8th, 10th and 12th graders were 2.1, 5.9 and 8.1%, respectively. The corresponding prevalences for OxyContin® were 1.8, 3.9 and 4.9%. The annual prevalences of nonmedical use of Vicodin® in college students and young adults were 3.8% and 6.3% in 2012. The corresponding numbers for OxyContin® were 1.2% and 2.3% (Johnston et al., 2012).

In summary, the aforementioned data from drug abuse surveys (NSDUH and MTF) collectively indicate high prevalence of abuse of HCPs among Americans including students thereby indicating their high abuse potential.
1.2.5. **Criterion 4: HCPs are related in their action to other schedule II opioid analgesics drugs.**

As described earlier in the document, hydrocodone is a semisynthetic opioid drug. Hydrocodone, similar to other opioid-like drugs, exerts its main pharmacological effects through binding to \( \mu \) opioid receptors (Gutstein and Akil, 2006). Similar to other morphine-like drugs, hydrocodone produces analgesia, suppression of cough reflex, respiratory depression, miosis and reduction in gastrointestinal motility and has the potential of being abused.

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 has an abuse liability similar to that of morphine.

In clinical studies, hydrocodone, similar to morphine, has been shown to produce euphoria and to suppress opioid withdrawal syndrome. Hydrocodone, similar to morphine, produces opioid withdrawal syndrome.

Recent clinical abuse liability studies have demonstrated that HCPs (Hycodan® or hydrocodone in combination with acetaminophen) are similar to morphine (schedule II) with respect to abuse liability related subjective effects (Zacny, 2003; Zacny et al., 2005; Wilsey et al., 2009). Another clinical study showed that hydrocodone and acetaminophen combination produced psychopharmacological effects that are similar to those of oxycodone and acetaminophen combination and acetaminophen alone did not differ from placebo in all measures (Zacny and Gutierrez, 2009).

1.2.6. **Other data sources**

Numerous individual state health and law enforcement offices have contacted the DEA expressing concerns about the severity of the HCPs diversion and abuse problem within their state. The Community Epidemiology Work Group Report (2012) to the National Institute on Drug Abuse continues to mention about the diversion and abuse associated with HCPs.

**Factor 1 Summary**

- Abuse liability of hydrocodone 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 HCPs (Hycodan® and hydrocodone and acetaminophen combination product) are substantially similar to those produced by morphine in humans.
- Hydrocodone and oxycodone in combination with acetaminophen, at equi-miotic doses, in general produced similar profile of psychopharmacological effects. These two opioid
products produced prototypic opiate-like effects and psychomotor impairment of similar magnitude.

- HCPs are the most commonly prescribed pharmaceutical opioids in the U.S.
- A review of drug abuse indicators for HCPs indicates that these products, similar to oxycodone products, are among the most widely diverted and abused drugs in the country.
- Forensic laboratory data (NFLIS and STRIDE) indicate that both HCPs and oxycodone products are the two most commonly diverted opioid analgesic drugs in the U.S.
- Data from DAWN indicate that the abuse of HCPs, similar to oxycodone products, is associated with large number of ED visits and deaths.
- Medical Examiner data from FDLE indicate that HCPs have been associated with large number of deaths in Florida.
- Data from NPDS indicate that annual toxic exposures involving HCPs consistently exceeded those for oxycodone products during 2001 through 2012.
  - The proportion (i.e., rates) of intentional single substance exposures relative to the total single substance exposures of all reasons for HCPs are slightly higher than that for oxycodone products.
  - Both HCPs and oxycodone products have rates higher than those for all pharmaceutical substances, all reported substances and for analgesic categories.
- Data from MTF indicate that a substantial percentage of young Americans (high school students) use HCPs for nonmedical purposes.

The above information collectively demonstrates that HCPs 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**

The HHS review provided scientific evidence of pharmacological effects of hydrocodone and other nonnarcotic active ingredients that are present in the currently marketed HCPs. The HHS states that hydrocodone is marketed primarily in fixed combinations with nonopioid drugs, namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine methylbromide.

Combination products of hydrocodone with acetaminophen and non-steroidal anti-inflammatory drugs (NSAIIDs) 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.

Hydrocodone, similar to other morphine-like drugs, selectively binds to μ opioid receptors. Receptor binding studies using cloned human μ, δ and κ opioid receptors showed that hydrocodone has higher affinity for μ opioid receptors than that for κ and δ opioid receptors (Kotzer et al., 2000). Binding affinity of hydrocodone (Ki = 19.8 nM) for μ opioid receptors in rat brain homogenates was higher than that of oxycodone (Ki = 47.4 nM) and codeine (Ki = 248 nM). In the same experimental conditions, morphine (Ki = 1.2 nM) and hydromorphone (Ki = 0.6 nM) had higher affinity than that of hydrocodone (Chen et al., 1991). Thompson and his associates (2004) reported that hydrocodone, oxycodone were ten-fold more potent than codeine in stimulating μ and δ opioid receptor-mediated G-protein activation using agonist-stimulated [35S]GTPyS binding in cells expressing the cloned human μ opioid receptors and expressing endogenous δ opioid receptors. DEA further notes a recent study by Volpe and his associates (2011) who investigated binding affinities of 19 approved opioid drugs using receptor binding assay in cell membrane preparation expressing recombinant human μ opioid receptors. These authors found that hydrocodone, oxycodone and morphine bind to μ opioid receptors with binding affinities of 41.58, 25.87 and 1.168 nM, respectively.

Because hydrocodone has high affinity for μ opioid receptors as compared to δ and κ opioid receptors, its analgesic and antitussive effects are mediated through activation of μ opioid receptors (HHS review). Acetaminophen and NSAIIDs are believed to increase the pain threshold by inhibiting prostaglandin synthesis via inhibition of distinct enzymes. Other potential mechanisms for acetaminophen may include inhibition of nitric oxide pathway and indirect activation of cannabinoid receptors. NSAIIDs are classified as mild analgesics and these are particularly effective in cases where inflammation produced sensitization of pain receptors to normally painless mechanical or chemical stimulus.

The HHS postulates two potential clinical rationales for combining analgesic substance such as hydrocodone with other analgesics present in HCPs: (i) increased effectiveness due to additive or synergistic effects between hydrocodone and NSAIIDs as a result of different mechanisms of actions of individual ingredients present in these combination products; (ii) decreased dose-related adverse reactions as a result of lower doses of the individual ingredients present in HCPs. While acetaminophen is well tolerated with a low incidence of gastrointestinal side effects, acute overdose can cause severe hepatic damage, coma and death.
The HHS states that opioids are recognized for their role in the management of pain. There are differences among opioid analgesics with regard to their pharmacokinetics, potency and adverse event profiles. Hydrocodone has high oral bioavailability. 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). The DEA notes that 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). The HHS also mentions that both acetaminophen and NSAIDs are less effective against severe pain, but have recognized efficacy in a variety of pain settings.

The HHS reviewed a published clinical study that assessed the efficacy of combination products in comparison to the individual components of combination products and noted that the HCP provided better pain relief as compared to hydrocodone or acetaminophen alone when “half pain gone”, but not the change in pain intensity from baseline, was used as a parameter (Beaver and McMillan, 1980). Similarly Beaver (1984) suggested that the combination of codeine and acetaminophen results in additive analgesic effect as compared to codeine and acetaminophen alone.

The HHS states that HCPs, similar to other opioid analgesics such as oxycodone products are associated with substantial number of overdose, suicide, abuse, and dependence reports. Overdose of HCPs, similar to other opioid analgesics, can lead to respiratory depression and death. According to the HHS, common adverse effects of NSAIDs include gastrointestinal, cardiovascular, renal and renovascular adverse events, and hepatic injury. Less common effects include thrombocytopenia, rashes, head ache, dizziness, and blurred vision. Acetaminophen has low incidence of gastrointestinal side effects and is a common household analgesic available over the counter. Overdoses of acetaminophen can cause severe hepatic damage and death. The combination products are linked to numerous liver injuries. The HHS also mentioned that 28% of one of the series of patients had taken opioid/acetaminophen combination products (HCPs make up over 60% of sales of prescription products containing acetaminophen).

The HHS also mentioned that hydrocodone in combination with either chlorpheniramine or homatropine is used as antitussive for the symptomatic relief of cough. Chlorpheniramine is an antihistamine and blocks H1 receptors. It also has anticholinergic and sedative properties. Chlorpheniramine prevents cold or allergy related symptoms such as sneezing, itchy or watery eyes, and runny nose. Homatropine methylbromide is an anticholinergic drug and is used in combination with hydrocodone at a supratherapeutic dosage to suppress deliberate overdosage.

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. Opioid analgesics have an important role in the management of pain. HCPs contain other nonnarcotic active ingredients such as acetaminophen, NSAIDs (aspirin and ibuprofen), chlorpheniramine or homatropine methylbromide. The mechanism of analgesic and antitussive effects of hydrocodone are different from those of nonnarcotic active ingredients present in HCPs. Acetaminophen and NSAIDs are less effective against severe pain, but have recognized role in a variety of pain settings.
3. **The State of Current Scientific Knowledge Regarding the Drug or Other Substance**

The HHS provided additional scientific information with focus on chemical and toxicological properties of hydrocodone and nonnarcotic components of HCPs. This information is summarized below.

Chemically, hydrocodone, also known as dihydrocodeinone, is 4,5-epoxy-3-methoxy-17-methylmorphinan-6-one, CAS [125-29-1], C₁₈H₂₁NO₃; 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 narcotic active ingredient in all HCPs that are currently marketed. 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. Lightheadedness, dizziness, sedation, nausea and vomiting are the most common side effects of hydrocodone. Other adverse effects of hydrocodone are constipation, rash, pruritus, euphoria, and dysphoria. Abuse of hydrocodone, similar to all opioids, may lead to tolerance to some or all of the adverse effects.

Acetaminophen is N-(4-hydroxyphenyl) acetamide, CAS [103-90-2]; C₈H₉NO₂; molecular weight 151.16. Other names of acetaminophen include 4-hydroxyacetonilide; p-hydroxyacetonilide; p-acetamidophenol; p-acetaminophenol; p-acetylaminophenol; N-acetyl-p-aminophenol; paracetamol. The most common adverse effects of acetaminophen are skin rash and other allergic reactions. The most serious adverse effect of acute overdosage of acetaminophen is dose-dependent, potentially fatal hepatic necrosis. Renal tubular necrosis and hypoglycemic coma may also occur. Hepatotoxicity may precipitate jaundice and coagulation disorders and progress to encephalopathy, coma, and death. In adults, ingestion of a single dose of 10 to 15 g (140 to 250 mg/kg) of acetaminophen may cause hepatotoxicity, while doses of 20 to 25 g are potentially fatal. During the first 2 days of acute poisoning by acetaminophen, symptoms do not reflect the potential seriousness of the intoxication. Nausea, vomiting, anorexia and abdominal pain occur within 24 hours following ingestion of a toxic dose and persist for a week, while clinical evidence of hepatic damage manifest within 2-4 days after ingestion.

Aspirin is also known as salicylic acid acetate; 2-acetoxybenzoic acid; acetyl salicylic acid; 2-(acetoxy) benzoic acid, CAS [50-78-2]; C₉H₈O₄; molecular weight 180.16. Aspirin occurs as needle-like crystals. It is odorless and in moist air it gets gradually hydrolyzed into salicylic and acetic acids and acquires the acetic acid odor. It is stable in dry air. The solubility of one gram of aspirin is as follows: dissolves in 300 milliliter (ml) of water at 25°C, 100 ml of water at 37°C, 5 ml alcohol, 17 ml chloroform and 10-15 ml ether. Aspirin is less soluble in anhydrous ether. Aspirin produces allergy to a portion of U.S. population. Ingestion of very small doses of aspirin can result in anaphylactic reactions in susceptible persons especially children and asthmatics. The major adverse effects of aspirin include nausea, vomiting, epigastric discomfort, gastrointestinal bleeding, tachypnea and hyperpnoea, tinnitus, deafness,
sweating, vasodilatation, hyperpyrexia (rare), dehydration, irritability, tremor, blurred vision, and subconjunctival hemorrhages.

Chlorpheniramine is also known as \( \gamma-(4\)-chlorophenyl\)-\(N,N\)-dimethyl-2-pidinepropanamine; 2-\(p\)-chloro-\(\alpha-(2\)-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)-3-\(N,N\)-dimethylpropylamine; \( \gamma-(4\)-chlorophenyl\)-\( \gamma-(2\)-pyridyl\)propyldimethylamine; chloroprophenpyridamine; CAS \([132-22-9]\), \(C_{16}H_{19}ClN_{2}\); molecular weight 274.79. According to HHS, the most common adverse effects of chlorpheniramine are related to its depressant effects on the central nervous system and these include drowsiness, lethargy, fatigue, hypnosis, and coma. Related effects include vertigo, ataxia, tinnitus (ringing in ears), and blurred vision. Initial sedation is often followed by central nervous system hyperexcitability. Excitation is often the first evidence of chlorpheniramine poisoning in children. The stimulant phase is associated with tremors, anxiety, insomnia, excitement, hallucinations, delirium, toxic psychosis, and convulsions. Dangerous hyperpyrexia may occur in children. Gastrointestinal effects include dry mouth, anorexia, nausea, vomiting, abdominal distress, constipation, and/or diarrhea.

Ibuprofen is also known as \( p\)-isobutylhydratropic acid; \((\pm)\)-2-(\(4\)-isobutylphenyl)propionic acid and \( \alpha\)-methyl-4-(2-methylpropyl) benzene acetic acid, CAS \([15687-27-1]\). \(C_{13}H_{18}O_{2}\), molecular weight 206.28. Ibuprofen is a colorless crystalline stable solid and is relatively insoluble in water and readily soluble in most organic solvents. Gastrointestinal effects are the most common adverse effects and include the following: epigastric pain, nausea, heartburn, and sensations of “fullness” in the gastrointestinal tract. Other less frequently reported adverse effects include thrombocytopenia, skin rashes, head ache, dizziness, and blurred vision. In few cases adverse effects include amblyopia, fluid retention, and edema. In ibuprofen overdose cases, primarily nausea and vomiting are experienced.

Homatropine methylbromide is chemically known as 8-azoibicyclo[3,2,1] octane, 3-[(hydroxyphenylacetyl)oxy]-8,8-dimethyl-, bromide, \( endo\); or as 3\(\alpha\)-hydroxy-8-methyl-1\(\alpha\)H,5\(\alpha\)H-tropanium bromide mandelate. It occurs as minute needles, is freely soluble in water and diluted alcohol; slightly soluble in absolute alcohol; and, insoluble in ether. The most common adverse effects of homatropine, atropine and other antimuscarinic are dose-related and are usually reversible upon therapy discontinuation. At therapeutic doses, adverse effects include dryness of the mouth with difficulty in swallowing and talking, thirst, reduced branchial secretions, mydriasis with cycloplegia, photophobia, flushing and dryness of the skin, transient bradycardia followed by tachycardia with palpitations and arrhythmias, and difficulty in micturition, reduction in tone and motility of gastrointestinal motility and constipation. In overdose, peripheral effects become more pronounced causing hyperthermia, hypertension, increased respiration, nausea and vomiting. Restlessness, confusion, excitement, ataxia, incoordination, paranoid, and psychotic reactions, hallucinations, delirium and seizures may also occur. In severe intoxication, CNS depression, coma, circulatory and respiratory failure, and death may occur.
Summary

Hydrocodone is a semisynthetic opioid. The bitartrate salt form of hydrocodone is the main active component in all currently marketed HCPs. Other nonnarcotic drugs present as co-ingredients are aspirin, ibuprofen, chlorpheniramine or homatropine. Hydrocodone and nonnarcotic drugs present in HCPs have potential to produce adverse effects.

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 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.

4.2. History and pattern of abuse following the enactment of the CSA

At the time the CSA was passed, HCPs were primarily utilized as cough suppressants. It was not until the 1990s that HCPs started to be widely used as an analgesic. This is evident from increase in total prescriptions for hydrocodone analgesic combination products (IMS Health’s NPA™ database). During this period, there was also corresponding increase in misuse and abuse of HCPs as indicated by data from national surveys, poison control centers, forensic laboratory and DAWN data (see Factor 1). Data from DEA field offices indicate that HCPs are diverted and are among the most sought after licit drugs in every geographic region of the country. The DEA case reports document the diversion of HCPs by pharmacy theft, doctor shopping, fraudulent oral (call-in) prescriptions, fraudulent or altered prescriptions, diversion by registrants and various drug trafficking schemes (see appendix 1 for brief summaries of a sampling of case files).

According to the DEA’s ARCOS data, until 2008, the annual distribution of HCPs (calculated as hydrocodone bitartrate salt) consistently exceeded that of oxycodone products (calculated as oxycodone hydrochloride). However, in 2010, annual distribution of oxycodone products exceeded that of HCPs. In 2011 and 2012, the annual distribution of HCPs is similar to that of oxycodone products. These amounts of HCPs and oxycodone products are the total amounts available for both medical and nonmedical use, as these drug substances are not clandestinely produced nor does the DEA has any evidence of that either drug is illicitly imported into the U.S. in any significant amount. In 2012, a total of about 68,430 kilograms of HCPs and a total of 68,004 kilograms of oxycodone products were distributed to end user registrants.
HCPs are abused by individuals of diverse ages from adolescents to older populations. In 2012, of the 37 million people in the United States who used pain relievers nonmedically in their lifetime, over 25.6 million (representing 9.9% of the U.S. population age 12 years or older) reported lifetime nonmedical use of HCPs. The MTF surveys indicate that from 2002 through 2012, 8.1 to 10.5% of high school seniors used hydrocodone for nonmedical purposes annually.

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 stated 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 a 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 HCPs is by far the most prevalent followed by other oxycodone products (oxycodone immediate release single-entity 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 nonmedical 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. These authors suggested that rates of abuse calculated as cases per 1000 patients who received a given opioid analgesic provide a measure of drug risk (abuse)-benefit (appropriate analgesia) profile.
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 rate of abuse was highest for HCPs at 3.75 per 100,000 population followed by oxycodone products at 1.81 per 100,000. HCPs were involved in 55% of all of the intentional exposure cases, whereas oxycodone products were involved in 27%. Following exclusion of suicide cases from the data analysis, HCPs was still the most commonly abused opioid. These authors discussed that higher rates of HCPs 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.

Forrester (2011) reviewed data on toxic exposure calls received by the Texas Poison Centers from 1998 through 2009 and found that toxic exposure calls related to the ingestion of combination of HCPs, carisoprodol and alprazolam, commonly referred under street names such “Holy Trinity,” “Houston Cocktail,” or “Trio”, have increased from 2000 through 2007 with some decline in 2009. Suspected attempted suicide accounted for 59.3% of cases while intentional misuse or abuse accounted for 27.3%.

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 HCPs as drugs of abuse increased in the 1990s coinciding with its increasing use as analgesic. Currently HCPs are widely diverted and abused throughout the U.S as demonstrated in national and regional drug abuse databases (see Factor 1 and Appendix 1). HCPs and oxycodone products (schedule II) are the two most common opioid analgesic products encountered by law enforcement.

5. The Scope, Duration, and Significance of Abuse

The HHS reviewed the scope, duration and significance of abuse of HCPs. The HHS states that both HCPs and oxycodone products have high potential for abuse, including the patterns of use and abuse as well as the rates and absolute numbers of events linked to misuse and abuse. The HHS mentions that hydrocodone abuse is considerable and is associated with considerable negative public health impact. The extent of nonmedical use of HCPs by adolescents is higher than for oxycodone products. These data are of significant concern as this may reflect particular risk for younger individuals.

The HHS also states that because of large number of prescriptions, large amounts of HCPs are potentially available for illicit use. Large number of adversely affected individuals and the severity of adverse effects related to abuse of HCPs suggest that individuals are taking these products in amounts sufficient to create a hazard to their health and to the safety of other individuals and the community. Abuse of HCPs is associated with progressively increasing trends in serious adverse effects, including ED visits, admissions for abuse treatment, and in
mortality data in selected states. The HHS cites the widespread prescriptions for HCPs as one of the reasons for these adverse outcomes. According to the HHS, these data collectively suggest that HCPs have high potential for abuse.

The DEA further notes that since the initial reports published in 1960s about abuse of hydrocodone in the United States (Rosenwald and Russel, 1961), its abuse has continued although widespread diversion and abuse of HCPs were not evident until the 1990s. By late 1990s, there were large increases in the diversion and abuse of HCPs.

Today, HCPs are associated with significant illicit activity and abuse. Federal, state and local forensic laboratory data rank HCPs as one of the two most frequently encountered opioid pharmaceuticals in submissions to the laboratories (see Factor 1). For example, in 2012, there were over 34,000 exhibits for HCPs (NFLIS). All divisions of the DEA across the U.S. have reported that HCPs are among the most sought after pharmaceuticals. In 2012, according to the poison control centers data (NPDS), there were over 29,390 toxic exposures involving HCPs. In 2002, there were over 25,000 DAWN ED visits associated with HCPs and these were ranked sixth among all controlled substances. According to DAWN, the nonmedical use related ED visits for HCPs were 86,258, 95,972, and 82,480 in 2009, 2010, and 2011, respectively. A number of data sources (See Factor 1) indicate that abuse of HCPs is associated with large number of deaths. For example, according to the HHS, DAWN medical examiner (ME) data for five States from 2004 through 2010 reported an increase of 63% and 133% in deaths related to HCPs and oxycodone products, respectively. According to the FDLE, HCPs have been associated with large numbers of deaths in Florida. For example, in 2012, HCPs were associated with 777 deaths, while oxycodone products were associated with 1,426. From 2006 through 2012, NPDS reported a total of 84,798 single substance exposures related to HCPs resulting in 195 deaths. The corresponding data for oxycodone products is 57,219 exposures and 173 deaths. According to NSDUH, there were large number of lifetime and past year initiates of HCPs for nonmedical purpose and these numbers exceeded those of oxycodone products. According to the MTF, about 8 to 10% of high school seniors reported nonmedical use of Vicodin®, a HCP, in recent years.

The Appendix 1 lists annotated case histories of a sampling of HCPs diversion cases characterized by DEA communications from its field offices from 1994 through 2013. These summaries reflect only those cases that were entirely federal or in which federal assistance was involved. Substantial numbers 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, fraudulent oral (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 HCPs and the amounts of HCPs diverted from legitimate channels are significant.

5.1 Pharmaceutical investigations data - DEA

Information regarding DEA cases involving diversion of HCPs and oxycodone products are obtained from two DEA Model 204 databases namely, the Case Status Database (CAST) that
contains information about DEA Cases and the Defendant Statistical System (DSS) database that contains information about its enforcement activities (i.e. arrest circumstances, charges, drug types, and dispositions).

Annual total cases involving diversion of HCPs consistently exceeded those for oxycodone products for years 2004 through 2007 (Table 17). However since 2008 cases involving oxycodone products consistently exceeded HCPs cases. This is consistent with larger increases in the total amounts of oxycodone products distributed annually compared to HCPs during this period as reported by IMS Health’s NSP™ database (Table 1). It is also important to note that law enforcement is more likely to legally pursue the investigations involving oxycodone products as these are schedule II products as compared schedule III HCPs. Cases (3,501) involving HCPs resulted in 3,658 arrests leading to 2,000 convictions, while cases (5,750) involving oxycodone products resulted in 10,952 arrests leading to 4,805 convictions from 2004 through 2013.

Table 17. Pharmaceutical investigations involving HCPs and oxycodone products$§$

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<td>322</td>
<td>196</td>
<td>280</td>
<td>553</td>
<td>206</td>
</tr>
<tr>
<td>2008</td>
<td>322</td>
<td>385</td>
<td>262</td>
<td>396</td>
<td>792</td>
<td>449</td>
</tr>
<tr>
<td>2009</td>
<td>348</td>
<td>469</td>
<td>298</td>
<td>572</td>
<td>1,129</td>
<td>607</td>
</tr>
<tr>
<td>2010</td>
<td>325</td>
<td>486</td>
<td>312</td>
<td>817</td>
<td>1,584</td>
<td>677</td>
</tr>
<tr>
<td>2011</td>
<td>417</td>
<td>444</td>
<td>209</td>
<td>975</td>
<td>2,257</td>
<td>675</td>
</tr>
<tr>
<td>2012</td>
<td>470</td>
<td>368</td>
<td>184</td>
<td>1,007</td>
<td>1,883</td>
<td>919</td>
</tr>
<tr>
<td>2013</td>
<td>455</td>
<td>386</td>
<td>113</td>
<td>1,086</td>
<td>1,859</td>
<td>800</td>
</tr>
<tr>
<td>Totals (2004-2013)</td>
<td>3,501</td>
<td>3,658</td>
<td>2,000</td>
<td>5,750</td>
<td>10,952</td>
<td>4,805</td>
</tr>
</tbody>
</table>

§The data (retrieved on January 13, 2014) are obtained from DEA Model 204 databases namely, the Case Status Database (CAST) that contains information about DEA Cases and the Defendant Statistical System (DSS) database that contains information about its enforcement activities (i.e. arrest circumstances, charges, drug types, and dispositions).

Summary

Initial reports of abuse of HCPs were published in 1960s. Since 1990s, the diversion and abuse of HCPs has escalated in the U.S. HCPs, similar to oxycodone products, are widely diverted and abused pharmaceutical opioid analgesic. DEA case investigations documented numerous methods of diversion of HCPs. These methods involved drug theft, doctor shopping, fraudulent oral (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 HCPs as antitussive and analgesic drugs, the misuse and abuse of these products present numerous 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 including deaths. According to the CDC, from 1999 to 2010, the number of drug poisoning deaths involving any opioid analgesic (e.g., oxycodone, methadone, or hydrocodone) markedly increased (over four-fold), from 4,030 to 16,651, and accounted for 43% of the 38,329 drug poisoning deaths and 39% of the 42,917 total poisoning deaths in 2010. In 1999, opioid analgesics were involved in 24% of the 16,849 drug poisoning deaths and 20% of the 19,741 total poisoning deaths (CDC, 2013). Similarly as discussed later in this section, both HCPs and oxycodone products are associated with large number of deaths in Florida.

Another important risk factor associated with HCPs is limited to nonnarcotic active ingredients and their potential to cause toxicity in high doses. According to the HHS review, all nonnarcotic active ingredients that are present in currently marketed HCPs have potential to cause adverse health consequences when ingested in large doses.

6.1. **FDA Adverse Event Reporting System (FAERS) data**

The HHS reviewed the HCPs related adverse events that were reported to the FDA Adverse Events Reporting System (FAERS) from 1969 through 2012 and compared with those associated with oxycodone products. The most common adverse events reported for HCPs included the terms such as complete suicide, intentional overdose, drug abuse, drug dependence, and drug abuser. The HHS found that both HCPs and oxycodone products are associated with substantial numbers of reports of overdose, suicide, abuse, and dependence reports. Both products have large numbers of adverse events reported that reflect abuse, misuse and injury due to inappropriate use and HCPs had fewer such reports than oxycodone products. However, the

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23 Drug poisoning deaths include unintentional or intentional poisoning deaths resulting from overdoses of a drug, being given the wrong drug, taking the drug in error, or taking a drug inadvertently.

24 Total poisoning deaths include those resulting from drugs, and those associated with solid or liquid biologics, gases or vapors, or other substances. Poisoning deaths are from all manners, including unintentional, suicide, homicide, and undetermined intent.

25 FAERS is a computerized information database designed to support FDA’s surveillance program for the post-marketing safety for all drug and therapeutic biologic products. FDA receives adverse drug reaction reports from manufacturers as required by regulation. Health care professionals and consumers voluntarily submit reports through MedWatch program. All reported adverse terms are coded according to the standardized international terminology, MedDRA (the Medical Dictionary for Regulatory Activities). These numbers are crude reports and may include duplicates. These reports were not individually reported to determine the association between the drug and the adverse event reported and may contain concomitant use of other medications.

26 The top 20 most frequently reported adverse event terms associated with all hydrocodone reports (a report may contain more than one adverse event) received from 1969 to 2012 in the FAERS, in decreasing frequency, were: Completed suicide, overdose, cardio-respiratory arrest, toxicity to various agents, cardiac arrest, respiratory arrest, drug ineffective, intentional overdose, nausea, intentional drug misuse, vomiting, death, drug abuse, accidental overdose, pain, dizziness, medication error, drug dependence, headache, and drug abuser.
HHS states that FAERS has several limitations and caution should be exercised in comparing drug safety issues.27

The DEA further notes that the following several factors need to be taken account when comparing adverse events associated with HCPs with those of oxycodone products. One important variable is FDA’s approval of new products for marketing. Numbers of FAERS 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 for the present review. For example, since the enactment of CSA in 1971, until recently there are no new NDA’s for hydrocodone28, while there were NDAs for oxycodone (e.g. approval of oxycodone high strength extended release single-entity product namely, OxyContin® in mid 1990s).

Another variable is the presence of drug products marketed 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 HCPs, is marketed with risk management program. Another variable, as mentioned in the HHS’s review, is the coverage in public media about adverse health effects. 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. 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).

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 (160 mg formulation was initially marketed, but was later withdrawn due to safety concerns) per each dose unit. Because adverse effects including ED visits, deaths and abuse/dependence producing properties of a given opioid analgesic are a function of its dose, such product is likely to possess higher potential to cause adverse effects than its moderate strength immediate release single-entity products or its low strength combination products. Consistent with this as mentioned later, 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

27According to HHS, “FAERS 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, in particular, 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 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. Some of the numbers may reflect duplicates.”

28In the United States there are currently no approved, marketed, products containing hydrocodone in combination with other active ingredients that fall outside the schedule III definition of the CSA. Further, until recently, there were no approved hydrocodone single-entity schedule II products. In Oct. 2013, the FDA approved Zohydro™ ER, a single-entity, extended release schedule II hydrocodone product. The sponsor of this product in a press release dated Oct. 25, 2013 stated that Zohydro™ ER will be launched in approximately four months. Accordingly, all of the historical data regarding hydrocodone from different national and regional databases as presented in this document should refer to HCPs only, regardless of whether the database utilizes the term “hydrocodone” or “hydrocodone combination products.”
OxyContin® as compared to the corresponding data among lifetime users of other oxycodone products (excluding OxyContin® lifetime users) or HCPs.

For the above mentioned reasons, DEA calculated the FAERS data (received from FDA) for oxycodone products other than OxyContin® by subtracting the FAERS data for OxyContin® from that of all oxycodone products. Also presented were the data for HCPs (Table 18). All adverse event data for these products was also presented temporally as 10-year blocks in Figure 1. According to this analysis, although adverse event reports received from 1969 through August 28, 2008 for all oxycodone products exceeded those for HCPs, 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 HCPs. Further majority of adverse events reported during this period (1969 - 2008) for HCPs (88%), OxyContin® (98%), all oxycodone products (96%), and oxycodone products other than OxyContin® (92%) started occurring in high frequency from 2001.

Table 18. FAERS data for HCPs, OxyContin®, oxycodone products, and oxycodone products other than OxyContin® reported since 1969 to August 28, 2008

<table>
<thead>
<tr>
<th>Drug</th>
<th>All Adverse Event Reports</th>
<th>Overdose Reports (% of All Adverse Event Reports)</th>
<th>Completed Suicide Reports (% of All Adverse Event Reports)</th>
<th>Abuse and Dependence Reports (% of All Adverse Event Reports)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPs</td>
<td>6,232</td>
<td>1,871 (30.0%)</td>
<td>1,152 (18.5%)</td>
<td>829 (13.3%)</td>
</tr>
<tr>
<td>OxyContin®</td>
<td>11,282</td>
<td>2,413 (21.4%)</td>
<td>149 (1.3%)</td>
<td>6,191 (54.9%)</td>
</tr>
<tr>
<td>All Oxycodone Products including OxyContin®</td>
<td>17,400</td>
<td>5,073 (29.2%)</td>
<td>873 (5.0%)</td>
<td>7,026 (40.4%)</td>
</tr>
<tr>
<td>Oxycodone Products other than OxyContin®</td>
<td>6,118</td>
<td>2,660 (43.5%)</td>
<td>724 (11.8%)</td>
<td>835 (13.6%)</td>
</tr>
</tbody>
</table>
Of particular importance is the finding that the primary risk factor for HCPs, 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 18). Further, the abuse and dependence reports associated with HCPs expressed as a percentage of its corresponding all adverse events (13.3%) were similar to those for oxycodone products other than OxyContin® (13.6%).

Majority of adverse events for both HCPs (88%) and oxycodone products (96%) were reported during 2000-2008. 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 2 and 3. 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 HCPs and oxycodone products other than OxyContin® were significantly smaller in magnitude as compared to those for OxyContin®. Further, the time-course curves for HCPs nearly overlapped with those for oxycodone products other than OxyContin®.
In summary, the adverse event report profile for HCPs 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” (HCPs) drug products demonstrates its risks for adverse health effects.

6.2. Drug Abuse Warning Network (DAWN)

According to the DAWN, as mentioned earlier, ED mentions associated with HCPs and oxycodone products are the highest among all opioid analgesics (see Factor 1). The rates of ED
mentions, calculated as the number of annual ED mentions per kilogram of drug distributed, for HCPs were slightly higher (1998 -2000), similar (for 2001) or lower (from 2002 through 2011) than the corresponding rates for oxycodone products (see Table 2 in Factor 1). It is important to note that in recent years there has been a rapid escalation of annual distribution of oxycodone products equaling with annual distribution of HCPs for the first time in 2009. In 2010, 2011 and 2012, annual distribution of oxycodone products surpassed that of HCPs (IMS Health’s NSP™ database). These data from DAWN suggest that both HCPs and oxycodone products have a large adverse risk to the public health.

According to the HHS, DAWN medical examiner (ME) data for five states from 2004 through 2010, reported an increase of 63% and 133% in deaths related to HCPs and oxycodone products, respectively.

6.3. Florida Medical Examiners’ data

According to the Florida Department of Law Enforcement (FDLE), HCPs have been associated with large numbers of deaths in Florida in recent years (see Factor 1).

6.4. Poison control centers data

According to the NPDS annual reports, since 2002, annual figures for toxic exposures (within the category of opioid analgesic drugs) were the largest for HCPs, followed by oxycodone products (see Factor 1). From 2006 through 2012, NPDS reported a total of 84,798 single substance exposures related to HCPs resulting in 195 deaths. The corresponding numbers for oxycodone products were 57,219 exposures and 173 deaths (Table 19). The rates of deaths (per 1000 single substance exposures), as calculated by using cumulative single substance exposure data from 2006 through 2012, for HCPs (2.3 deaths) and for oxycodone products (3.0 deaths) are over 4-fold and 5-fold higher than the corresponding rate associated with single substance exposures for all pharmaceutical substances combined (0.54 deaths per 1000 single substance exposures), respectively. The above data from NPDS suggest that both HCPs and oxycodone products have a large adverse risk (fatality) to the public health and such risk is considerably higher than that for all pharmaceuticals combined.
Table 19. Annual single substance toxic exposures and related fatalities involving HCPs and oxycodone products (from NPDS annual reports)

<table>
<thead>
<tr>
<th>Year</th>
<th>HCPs</th>
<th>Oxycodone products</th>
<th>All pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single substance exposures</td>
<td>Deaths</td>
<td>Deaths/1000 single substance exposures</td>
</tr>
<tr>
<td>2006</td>
<td>10,061</td>
<td>17</td>
<td>1.69</td>
</tr>
<tr>
<td>2007</td>
<td>11,001</td>
<td>23</td>
<td>2.09</td>
</tr>
<tr>
<td>2008</td>
<td>11,834</td>
<td>21</td>
<td>1.77</td>
</tr>
<tr>
<td>2009</td>
<td>12,559</td>
<td>31</td>
<td>2.47</td>
</tr>
<tr>
<td>2010</td>
<td>12,541</td>
<td>30</td>
<td>2.39</td>
</tr>
<tr>
<td>2011</td>
<td>13,756</td>
<td>37</td>
<td>2.69</td>
</tr>
<tr>
<td>2012</td>
<td>13,046</td>
<td>36</td>
<td>2.76</td>
</tr>
<tr>
<td>Totals (2006-2012)</td>
<td>84,798</td>
<td>195</td>
<td>2.30</td>
</tr>
</tbody>
</table>

In summary, both HCPs and oxycodone products are associated with significant public health risks.

7. *I*TS *P*SYCHIC OR *P*HYSILOGICAL *D*EPENDENCE *L*IABILITY

7.1. *A*nal*O*animal *s*tudies

7.1.1. *D*ependence liability of hydrocodone

Deneau and 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 the results obtained in humans (Seevers and Deneau, 1956). Deneau, McCarthy and Seevers (1959) further reported that hydrocodone is more potent than morphine in suppressing morphine abstinence in monkeys and equipotent to morphine in humans.

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 dependence liability for hydrocodone in humans (Tomkins et al., 1997).

7.1.2. Dependence liability of HCPs

The above mentioned animal studies predict that hydrocodone, similar to other schedule II opioid analgesics, has potential to cause severe psychic or physiological dependence and are consistent with the placement of hydrocodone 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 HCPs in animals. However, recent clinical studies as discussed later in this section indicate that HCPs produce abuse liability related pleasant effects as well as unpleasant effects that are substantially similar to those produced by morphine and oxycodone/acetaminophen combination. Further, acetaminophen, the nonnarcotic active ingredient present in majority (over 90% in kilogram amounts; IMS Health’s NSP™ database) of HCPs lacks psychoactive effects in recreational opioid abusers. These data suggest that HCPs upon chronic use have potential to produce dependence similar to that produced by hydrocodone.

7.2. Human studies

7.2.1. Dependence liability of hydrocodone

The HHS reviewed the two published clinical studies related to dependence liability assessment of hydrocodone (Fraser and Isbell, 1950; Jasinski and Martin, 1967). According to the HHS, Fraser and Isbell (1950) had found that hydrocodone completely relieves morphine withdrawal symptoms and the overall abuse liability of hydrocodone is nearly comparable to the addiction liability of morphine. Similarly, Jasinski and Martin (1967) study found that hydrocodone substitutes for morphine and diminishes the intensity of morphine withdrawal symptoms, although it was less potent than morphine with a ratio of 1.6/1 mg of hydrocodone to morphine.

The DEA further notes that 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.”

As stated by the HHS, in early human studies conducted in the U.S., hydrocodone has been shown to produce a sharp decline in the intensity of the opioid withdrawal symptoms and completely relieve withdrawal symptoms for 6 to 8 hours. The DEA notes 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 (Isbell, 1949; Fraser and Isbell, 1950). 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. Jasinski and Martin (1967) using double-blind clinical study 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 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.

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. Dependence liability of HCPs

7.2.2.1. Treatment Episode Data Set (TEDS)

The HHS reviewed data on admissions to the addiction treatment centers as reported in the Treatment Episode Data Set (TEDS) database for opiates, including HCPs and oxycodone products. TEDS reports data for the major (primary) drug of abuse (including opioids, alcohol, marijuana, stimulants) as well as up to two other drugs. In 2011, opiates other than heroin were mentioned as the primary drugs of abuse in 186,986 admissions to treatment centers. The HHS found that from 2004 through 2011, admissions related to oxycodone products as the primary drug of abuse are higher than those for HCPs, but both drugs are mentioned frequently as being

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29 TEDS is a program coordinated and managed by the 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 includes information on demographic variables including age, gender, race and ethnicity. TEDS also reports on the top three drugs of abuse at the time of admission. TEDS does not include all drugs that may have been abused prior to admission. States and jurisdictions can choose whether or not to report the detailed listing.

30 It is important to note that as discussed elsewhere in the document, oxycodone combination products other than
abused. In a subset data from 20 states, the admissions related to HCPs as the primary drug of abuse increased from 2010 to 2011. The HHS also found that admissions that list HCPs as one of the several drugs of abuse are also common. Admissions related to HCPs as the primary drug of abuse are higher than that of the number related to hydromorphone, a schedule II opioid drug.

7.2.2.2. National Survey on Drug Use and Health (NSDUH)

The HHS’s 2008 review analyzed NSDUH data from 2002 through 2005 with regard to the number of individuals that met criteria for substance use disorder (abuse or addiction)\(^{31}\) on any pain relievers among lifetime users of different narcotic analgesics products and found that individuals who used oxycodone products nonmedically in their lifetime develop a substance use disorder at a higher rate than those who used HCPs. In order to adjust for OxyContin-specific data, for the reasons mentioned earlier (see Factors 1 and 6), the DEA expanded this analysis by obtaining from the SAMHSA additional data from 2002 through 2006 (Table 20). 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 20 and are presented in Figure 4.

The NSDUH 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 HCPs were 1.01 and 1.23 million, 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 20).

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 HCPs (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 HCPs (Table 20 and Figure 4).

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), HCPs (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).

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\(^{31}\) 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.
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 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.

Table 20. Lifetime nonmedical users of any pain relievers, HCPs, 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

<table>
<thead>
<tr>
<th>Data Type</th>
<th>Drug Category</th>
<th>Numbers in Thousands (Percentages)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2002</td>
</tr>
<tr>
<td><strong>Lifetime Users of</strong></td>
<td>Any Pain Reliever</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>29,611</td>
</tr>
<tr>
<td></td>
<td>HCPs&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>13,952</td>
</tr>
<tr>
<td></td>
<td>OxyContin®</td>
<td>1,924</td>
</tr>
<tr>
<td></td>
<td>Oxycodone Products&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>10,151</td>
</tr>
<tr>
<td></td>
<td>Oxycodone Products Other than OxyContin®</td>
<td>8,227</td>
</tr>
<tr>
<td><strong>Past Year Abuse or Dependence</strong></td>
<td>Any Pain Reliever</td>
<td></td>
</tr>
<tr>
<td>on Any Pain Reliever</td>
<td></td>
<td>1,509</td>
</tr>
<tr>
<td>Among Lifetime Users of</td>
<td></td>
<td>(5.1)</td>
</tr>
<tr>
<td></td>
<td>HCPs&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>1,042</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7.4)</td>
</tr>
<tr>
<td></td>
<td>OxyContin®</td>
<td>399</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(20.7)</td>
</tr>
<tr>
<td></td>
<td>Oxycodone Products&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>876</td>
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<td></td>
<td></td>
<td>(8.6)</td>
</tr>
<tr>
<td></td>
<td>Oxycodone Products Other than OxyContin®</td>
<td>477</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5.8)</td>
</tr>
</tbody>
</table>

*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.

<sup>1</sup>Includes other-specific drug responses that are not asked about explicitly in the Pain Relievers module but fall into this category.

<sup>2</sup>Includes Vicodin®, Lortab®, or Lorcet®, and hydrocodone.

<sup>3</sup>Includes Percocet®, Percodan® or Tylox®, and OxyContin®.

<sup>§</sup>In the U.S., nearly 100% (of total kilogram amounts distributed) of HCPs was marketed as combination products that contain hydrocodone in combination with nonnarcotic active ingredients namely acetaminophen, aspirin, ibuprofen, chlorpheniramine or homatropine, while oxycodone products were marketed both as single-entity (over 70% of total kilogram amounts distributed) and combination products (over 20% of total kilogram amounts distributed).
7.2.2.3. FDA Adverse Event Reporting System (FAERS)

The HHS review provided the results of their analysis of Adverse Event Reporting System (FAERS) data for abuse/dependence producing properties of HCPs and oxycodone products. Using these data, the HHS review concluded that abuse/dependence ranking for HCPs is lower than that of oxycodone products. The DEA notes that, as discussed earlier (see Factor 6), The HHS also cited a number of limitations of FAERS database. 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, the DEA calculated the FAERS data for oxycodone products other than OxyContin® by subtracting the FAERS data for OxyContin® from that of all oxycodone products. Also presented were the data for HCPs (see Table 18, and Figures 1, 2 & 3 in Factor 6). According to this analysis, although adverse event reports received from 1969 through August 28, 2008 for all oxycodone products exceeded those for HCPs, 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 HCPs.
Of particular importance is the fact that the abuse and dependence reports associated with HCPs 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 18).

Majority (over 95%) of abuse and dependence events for both HCPs and oxycodone products were reported mainly from 2001. 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 5. 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 HCPs and oxycodone products other than OxyContin® were significantly smaller in magnitude as compared to those for OxyContin®. Further, the time-course curves for HCPs nearly overlapped with those for oxycodone products other than OxyContin®. These data indicate that abuse and dependence reports, expressed as percent of all adverse events, for HCPs are similar to those for oxycodone products other than OxyContin® and are considerably less than those for OxyContin®.

7.2.2.4. Data submitted by the petitioner

The petitioner provided data regarding patient admissions to his treatment facility and stated that HCPs have 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 HCPs 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.”

7.2.2.5. Published scientific and medical reports

The DEA notes that recent clinical studies investigated reward related subjective effects of two HCPs namely Hycodan® and hydrocodone in combination with acetaminophen (Zacny 2003; Zacny et al., 2005; Wilsey et al., 2009; Zacny and Gutierrez, 2009). These studies found that both these HCPs produce abuse liability related subjective effects that are substantially similar to those produced by morphine and oxycodone/acetaminophen combination (see Factor1). Zacny et al. (2005) reported that acetaminophen, a nonnarcotic active ingredient present in majority (over 90% in kilogram amounts, IMS Health’s NSP™ database) of HCPs, lacks psychoactive effects in recreational opioid abusers. 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. Zacny and Gutierrez (2009) found that hydrocodone/acetaminophen and oxycodone/acetaminophen at equi-miotic doses, in general, produced similar profile of psychopharmacological effects. These two opioid products produced prototypic opiate-like effects and psychomotor impairment of similar magnitudes. These findings with hydrocodone and oxycodone combination products are almost identical to those reported for the single-entity products containing hydrocodone and oxycodone (Walsh et al., 2008). Wilsey et al. (2009) reported that effects of extended release morphine on the markers of drug liking/abuse liability did not significantly differ from that of hydrocodone/acetaminophen combination in chronic pain patients with history of prescription opioid abuse.

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 HCPs 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 products (89% for controlled release products and 81% for immediate release products) and HCPs (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 products (71%), and HCPs (67%) followed by immediate release oxycodone products (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 HCPs (16%), methadone (16%), controlled release oxycodone products (15%) and immediate release oxycodone products (13%). Among primary prescription opioid abusers the most frequently cited primary opioids were controlled release oxycodone products (47.4%) and HCPs (24%) followed by methadone (8.2%) and immediate release oxycodone products (7.1%), morphine (6.3%), hydromorphone (5.1%), fentanyl (0.9%), other opioid (0.8%) and buprenorphine (0.1%).

Cicero et al. (2010) surveyed 1,818 prescription opioid dependent patients entering drug treatment centers (geographically balanced with good representation of large urban, suburban and rural treatment centers) and found that HCPs and oxycodone products were the drugs of choice in 75% of patients, while potent μ opioid agonists such as fentanyl, hydromorphone and morphine were rarely chosen (<5% each).

Butler and his associates (2011), using computer-assisted addiction Severity Index, evaluated the abuse risk of 11 prescription opioid compounds/formulations in 59,792 patients entering into treatment for substance use disorders at 464 treatment facilities in 34 states. These authors found that highest risk of abuse (unadjusted for prescription availability) was associated with HCPs, and immediate release oxycodone products. However, when adjusted for prescription availability, risk of abuse for both HCPs and immediate release oxycodone products, but not extended release oxycodone products, are less than all other prescription opioids, with the exception of methadone.
The above mentioned epidemiological data from published studies are consistent with the data from TEDS, NSDUH and FAERS databases and from clinical studies. These data collectively indicate that HCPs, similar to oxycodone products, have 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 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 HCPs, similar to schedule II drugs, 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**

HCPs are not immediate precursors of any substance controlled under the CSA, as defined in 21 U.S.C 811(e).

**IV. Findings for Schedule Placement Pursuant to 21 U.S.C. 812(b)**

21 U.S.C. 812(b) requires the evaluation of a substance’s abuse potential, accepted medical use, and safety for use under medical supervision and psychic and physiological dependence for scheduling under the CSA. After consideration of the above eight factors determinative of control of a substance (21 U.S.C. § 811(c)), and a review of the scientific and medical evaluation and scheduling recommendation provided by the HHS, DEA finds that HCPs as summarized below meet the following criteria for transfer from Schedule III to Schedule II of the CSA, under 21 U.S.C. 812 (b)(2).

**A. HCPs have a high potential for abuse.**

The HHS states that hydrocodone is a full μ opioid receptor agonist. Scientific literature indicates that abuse liability of hydrocodone 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.

Recent clinical studies showed that physiological effects, subjective effects and drug “liking” scores produced by HCPs (Schedule III; Hycodan® and hydrocodone and acetaminophen combination product) are substantially similar to those produced by morphine (Schedule II), and oxycodone/acetaminophen combination (schedule II) in humans.

The HHS reviewed the DAWN data and found that the nonmedical use of HCPs is associated with large numbers of ED visits in the U.S. Based on these data and the severity of the adverse effects thereby suffered by the individuals who abuse these products, the HHS concluded that individuals are taking these products in amounts sufficient to create a hazard to
their health, or to the safety of other individuals or the community. The HHS stated that HCPs were mentioned in 82,479 ED visits and were listed in 3,376 admissions for drug treatment as the primary drug of abuse and in 6,601 admissions listing HCPs in addition to other drugs in 2011. The HHS also states that nationwide estimates of overdose deaths due to HCPs cannot be quantified, but the available data for a limited number of states suggest that HCPs contribute to a substantial numbers of overdose deaths each year.

The HHS mentions that there are increasing trends for adverse effects of abuse of HCPs, including ED visits, admissions to addiction treatment centers, and deaths in selected states. The HHS also states that special circumstances related to prescribing of HCPs underlie this increasing trend. HCPs are prescribed in an unprecedented manner and its total prescriptions exceed prescriptions for any other opioid analgesics and this characteristic drives its abuse potential and sets it apart from other opioid analgesics in terms of abuse risks. The HHS further adds that oxycodone products have lower numbers of prescriptions than that for HCPs, but have a higher potential for the development of abuse. However, the adverse effects on public health for both HCPs and oxycodone products are considerable.

A review of drug abuse indicators for HCPs over the past several years indicates that these products, similar to oxycodone products, are among the most widely diverted and abused drugs in the country. Data from NSDUH indicate that of the 37 million U.S. population who used pain relievers nonmedically in their lifetime, over 25.6 million reported lifetime nonmedical use of HCPs, while over 16 million reported nonmedical use of oxycodone products in 2012. Further, past year initiates of HCPs are substantially higher than that of oxycodone products. According to a report by NSDUH, the combined data from 2002 through 2005 indicate that 57.7% of persons who first used pain relievers nonmedically in the past year used HCPs and 21.7% used oxycodone products. According to the NSDUH, percentages of the lifetime users of HCPs reporting past year use of any pain reliever for nonmedical purpose are higher than those of the lifetime users of oxycodone products other than OxyContin® (i.e., oxycodone immediate release single-entity products and immediate release combination products) from 2002 through 2006. Data from MTF survey indicate that a substantial percentage of young Americans (high school students) use HCPs for nonmedical purposes.

Emergency Department (ED) visits data from DAWN database indicate that the rates of nonmedical use related adverse health consequences (calculated as annual ED visits per kilogram amount of drug distributed) for HCPs, depending on the year, are slightly higher, similar to, or slightly lower than the corresponding data for oxycodone products. Poison control centers data (from 2002 through 2012) from TESS and NPDS databases indicate that annual figures for toxic exposure (within the category of opioid analgesic drugs) were the largest for HCPs, followed by oxycodone products. Rates of annual toxic exposures per kilogram of HCPs distributed were slightly higher than that of oxycodone products. Annual rates of abuse and misuse (calculated as intentional toxic exposures expressed as percent of all types of toxic exposures) of HCPs are slightly higher than the corresponding rates for oxycodone products. Medical Examiner data from FDLE indicate that HCPs have been associated with large number of deaths in Florida. The rates of deaths (calculated as annual deaths per each kilogram of drug distributed in Florida) associated with HCPs, depending on the year, are similar to or slightly higher than those for oxycodone products.
Forensic laboratory data from NFLIS and STRIDE databases indicate that both HCPs and oxycodone products have been consistently reported as among the top ten most frequently encountered drugs over the past ten years and these are the leading diverted controlled pharmaceuticals among opioid analgesic drugs. The rates of diversion (calculated as cases or exhibits per each kilogram of drug distributed) of HCPs, depending on the year, are largely similar to, or slightly higher, or lower than those of oxycodone products (Schedule II).

The above data and information collectively indicate that HCPs, similar to oxycodone products, have high potential for abuse.

**B. HCPs have a currently accepted medical use in treatment in the United States.**

According to the HHS, several pharmaceutical products containing hydrocodone in combination with acetaminophen, aspirin, NSAIDS, and homatropine are approved by FDA for use as analgesics for pain relief and for the symptomatic relief of cough and upper respiratory symptoms associated with allergies and colds. Thus HCPs have a currently accepted medical use in treatment in the United States.

**C. Abuse of HCPs may lead to severe psychological or physical dependence**

According to the HHS, data from animal and human studies indicate the dependence potential of hydrocodone. The severe dependence potential of HCPs is reflected by the number of individuals admitting to the addiction treatment centers citing hydrocodone as their substance of abuse.

The NSDUH data from 2002 through 2006 indicate that the propensity of the lifetime users of HCPs to develop substance use disorder on any pain relievers is higher than that of lifetime users of any pain relievers, and lifetime users of oxycodone products other than OxyContin® (i.e., oxycodone immediate release single-entity products and immediate release combination products). The FAERS data indicate that the abuse and dependence reports associated with HCPs expressed as a percentage of its all adverse events was similar (both in magnitude and temporal distribution) to that for oxycodone products other than OxyContin®.

Several published epidemiological surveys and retrospective review of medical records of addiction treatment populations indicate that HCPs are among the most abused opioid pharmaceuticals in prescription opioid dependent individuals in the country and are frequently mentioned as the primary drug of abuse in these subjects.

The above data collectively indicate that, HCPs, similar to oxycodone products, have high potential to cause severe psychological or physiological dependence.
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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.

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

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 HCPs (among others) over a two year period. No valid prescriptions or physicians were utilized.

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

A physician was indicted for writing prescriptions for HCPs (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.

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.

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

A male pharmacist was arrested for delivery of HCPs 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 HCPs and 249 bottles of hydrocodone syrup for personal use. The veterinarian admitted to consuming 65 tablets of HCPs per day.
A male physician was arrested for distributing HCPs 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 HCPs, himself.

A female physician was arrested for obtaining HCPs (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 HCPs for personal use utilizing the clinic’s 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 HCPs 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 HCPs to a local street level drug trafficker. The drug cache was intercepted. Seizure of the pharmacist’s car revealed another 995 dosage units of HCPs.

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 HCPs 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 HCPs for personal use.

A female pharmacy technician was arrested for passing forged prescriptions for HCPs. 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 HCPs.
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 HCPs (among others). A search of the owner’s home revealed another 14,928 dosage units of HCPs (among others). The owner was distributing the drugs for street sales.

A male pharmacist was arrested for stealing over 10,000 dosage units of HCPs (among others) over a 14 month period.

A male pharmacist was arrested for illegally obtaining HCPs by use of stolen prescription pads from three physicians in the area.

A male physician and “Chief of Staff” at an University Medical Center was arrested for illegally obtaining HCPs by using bogus prescriptions written for a 92 year old patient residing in an assigned living center. The doctor admitted self-use of the HCPs.

A male pharmacist and owner of a pharmacy in the Houston area pled guilty to illegal delivery of HCPs. He was considered Houston’s most prolific diverter of HCPs and the 8th largest volume HCPs purchaser in the United States.

A male high school teacher was arrested for selling HCPs 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 HCPs. 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 HCPs. 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 HCPs which were being used by his addicted brother-in-law.

A male attorney was arrested for fraudulently writing prescriptions and acquiring the HCPs 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. Videotaped evidence showed that the physician was providing prescriptions in exchange for sexual favors.

A male pharmacist was arrested for diverting and selling HCPs over a two year period. Two hundred tablets of HCPs were sold for $750 on several occasions.

A male physician was arrested after writing prescriptions for HCPs 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 HCPs for sale. Multiple undercover purchases were made.

A male physician and attorney was arrested for selling over 5,000 dosage units per month of HCPs 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 HCPs 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 HCPs and mailing them to other individuals.

A male dentist pled guilty of misrepresentation and diversion of HCPs. The physician was writing prescriptions after revocation of his license to practice. He dispensed prescriptions for over 3,000 dosage units of HCPs 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 HCPs 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 HCPs in a “sex for drugs” scheme. The physician provided 5 prescriptions of HCPs, 100 tablets per Rx, in two different names to an undercover agent. 

A female pharmacy technician was arrested for diverting HCPs from her employer. 

A male pharmacy technician was arrested after video tapes showed him diverting HCPs 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 HCPs for his personal use. 

A male pharmacy technician was convicted of diverting HCPs. 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 HCPs (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 HCPs “day after day”. The prescriptions were dispensed in his wife’s name. The daily
A female registered nurse was arrested for fraudulent “phone in” prescriptions for HCPs 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 HCPs, 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 HCPs 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 HCPs 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 HCPs (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 HCPs 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 HCPs 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 HCPs from a pharmacy. A total of 37,000 dosage units were diverted in a 6 month period.

A pharmacy technician was arrested for dispensing HCPs 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 HCPs and intent to illegally sell the drug via the postal system.

A registered pharmacist was arrested for theft and diversion of HCPs from his pharmacy.

A federal jury convicted a physician for illegal distribution of drugs including HCPs.

A medical office assistant was arrested and admitted to fraudulently “phoning in” prescriptions for HCPs on five separate occasions.

An unemployed housewife was arrested and admitted to fraudulently “phoning-in” prescriptions for HCPs for both herself and her husband.

A male pharmacy technician was arrested for fraudulently prescribing HCPs 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 HCPs. 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 HCPs 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 HCPs 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 HCPs. 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 HCPs; while on bail from the original charges, the female had obtained an additional 240 dosage units of HCPs 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 HCPs 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 HCPs. The physician had written prescriptions for approx. 312,000 tabs of HCPs and had purchases at least 8,000 tablets of HCPs from pharmaceutical distributors. Local prices of HCPs 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 HCPs, 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 nonmedical purposes; and 11 counts of omitting material on required records.

A male registered pharmacist was arrested for unlawful distribution and dispensing of HCPs. A juvenile was interviewed after arrest for selling HCPs 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 HCPs 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 HCPs and for dispensing controlled substances without prescriptions. A 16 month audit revealed shortages of 4,400 dosage units of HCPs (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 HCPs, 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 HCPs. Undercover officers obtained prescriptions without presenting any medical complaint. As detailed in the medical record, HCPs were 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 HCPs. 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 (HCPs) 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 longtime 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 HCPs 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 HCPs 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 HCPs. 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 year old male was arrested for writing and processing forged prescriptions for HCPs 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 HCPs from the manufacturer and had diverted 10-12 bottles of HCPs (especially Lorcet 10/650).

DEA received intelligence that a 54 year old male was a major distributor of HCPs in Broward and Palm Beach counties. The individual was arrested upon delivering 5 sealed bottles of HCPs (2,500 tablets) to an undercover agent. A search of the individual’s vehicle revealed two additional sealed bottles of HCPs (1,000 tablets) and Xanax (1,000 tablets). During December an undercover agent had purchased three other sealed bottles of HCPs (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 HCPs 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 HCPs (Loracet) and a benzodiazepine (Lorazepam) and their generic equivalents (Lortab 10 mg: 17,244; HCPs 7.5: 200; Loracet + 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 HCPs 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 included HCPs (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 HCPs 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 HCPs, 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 HCPs. 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 HCPs 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 HCPs were deleted from the files. An additional 7 prescriptions totaling 300 tablets was also discovered.
A 40 year 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 HCPs 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.

This is an investigation of a female who habitually uses bogus “call-in” prescriptions to obtain HCPs. 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 HCPs by fraud.

An 18 year old female pharmacy technician admitted to and was arrested for supplying HCPs 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 HCPs. 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 HCPs tablets during a 3 month period. The MA was taken into custody after a bond reduction hearing for 1 count of trafficking HCPs. Through false prescriptions she fraudulently obtained, among others, 900 dosage-units of HCPs.

A female registered nurse was arrested for two counts of prescription forgery (state charges) which included HCPs. She was confronted by authorities and was found to have controlled substances in her possession in her purse including prescriptions for HCPs. 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 HCPs. On two occasions the individual sold stolen HCPs to a cooperative source. A subsequent search warrant resulted in seizure of 40 HCPs tablets, marijuana, money, a gun, and paraphernalia.
A veterinarian was arraigned on ten counts of obtaining possession of a controlled substance, HCPs, 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 (HCPs) 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 milliliters 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, HCPs, 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 HCPs 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 one count of HCPs 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 HCPs.
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 HCPs 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 products (SCH II) and HCPs (SCH III) on three occasions.

A woman was sentenced for illegally obtaining approximately 6,000 dosage units of HCPs 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 product) and 9 counts of unlawful distribution of HCPs (Lorcan 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 HCPs 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 HCPs.

A medical doctor was arrested for state charges of obtaining HCPs by deception. The doctor had previously admitted diverting quantities of HCPs 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 HCPs (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 HCPs (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 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 tablets.

An individual pled guilty to diverting in excess of 7,000 dosage units of HCPs 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 HCPs 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 HCPs. HCPs were 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 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.

A 257 count federal grand jury indictment was handed down for a pharmacy owner for diverting thousands of dosage units of HCPs (Hycodan® and Alexsia). 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.

A woman pled guilty for possession with intent to distribute HCPs. The woman was an employee of a pharmacy. An accountability audit covering 8 months was conducted and revealed shortages of 10,775 HCPs 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 without legitimate medical purposes.

A medical doctor was sentenced for possession of an excess of 15,000 dosage units of HCPs.

A medical doctor was convicted of knowingly and intentionally distributing 298 prescriptions for Vicodin ES 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 HCPs (Lortab and Tussionex) 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, 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 HCPs 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, Tylenol #3 and #4, Valium and Xanax.

A registered pharmacist was indicted on five charges of acquiring Lortab 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) 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).

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 HCPs.

A dentist was sentenced to five years of probation and $750 fine and 160 hours of community service for unlawful prescribing of Lortab (7.5 mg).

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 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 HCPs from her employer, Walmart Pharmacy.

**New cases added on March 20, 2008 and January 10, 2014**

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 HCPs 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 HCPs tablets. Information from DEA press releases was used as source for some cases.

In early 2004, a Pharmacist was arrested and charged with illicit distribution of 14,300 HCPs 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 HCPs.

In early 2004 investigators noted a pharmacy that was selling an inordinate amount of controlled substances, 80-90% of which were for HCPs. In just 18 months, the pharmacy had ordered over 7.3 million dosage units of HCPs. 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 HCPs, oxycodone product, 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 HCPs.

In July 2004, an owner and operator of a pharmacy in Pittsburg, PA, pled guilty to illegally dispensing HCPs. 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 HCPs 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 HCPs 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 product, HCPs, 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 product, HCPs, 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 HCPs 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 HCPs, 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 HCPs 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 HCPs from the hospital pharmacy on a weekly basis. Suspected quantities of HCPs included three to six 500 count bottles per week.

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 HCPs. The suspect stated that he uses some of the pills for pain, and sells the remaining. The suspect trades cocaine for the HCPs, which is obtained from a person who works in a local pharmacy.

In November 2005, guilty pleas to conspiracy to distribute HCPs 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 HCPs, 9,500 D.U. of alprazolam and 22 pounds of marijuana were located and seized. The controlled substances were destined for Eunice, Louisiana.
Following multiple undercover purchases a Physician was arrested for illicit distribution of HCPs, oxycodone product and phendimetrazine. During December 2005, the Physician purchased over 40,000 dosage units of HCPs.

In May 2006, an individual was arrested following the undercover purchase of 2,000 Vicodin, 10,000 Valium and 700 OxyContin® tablets.

In June 2006, following undercover purchases of 2,500 HCPs tablets and additional purchases of 4,000 tablets, DEA arrested two individuals. One individual was employed as a pharmacy technician.

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 HCPs associated with this case.

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 HCPs, which totaled 192,480 dosage units. DEA STRIDE system reported 351,508 tablets of HCPs seized.

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 HCPs (primarily Lorcet and Vicodin ES).

After the arrest of a Physician by DEA in November 2006, patients began visiting another Physician for diversion of HCPs via illicit prescriptions. Undercover purchases were made by DEA and an arrest warrant was issued for the second Physician for illicit distribution of HCPs.

In April 2007, a federal search warrant was executed at a residence in Tyler, Texas. Several thousand tablets of HCPs and alprazolam were seized. Multiple 500 count bottles of HCPs were kept at the residence. The suspect has talked of purchasing 5,000 tablets at a time from a source in Houston, Texas.

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 HCPs associated with this case.

In May 2007, subsequent to a traffic stop, a person was arrested in possession of approximately twenty six pounds of HCPs tablets. The suspect stated that the HCPs was obtained in Grand Prairie, Texas and was being transported to Jackson, Mississippi.

In June of 2007 a HCPs distributor agreed to pay $800,000 in fines pursuant to a consent judgment for distribution of over 9 million dosage units of HCPs to 18 rogue internet pharmacies for filling of prescriptions in absence of Doctor-Patient relationship.

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 HCPs and 234,000 dosage units of alprazolam from July 2006 through June 2007.

In June 2007, a person admitted perpetrating the theft of a commercial tractor-trailer transporting over 16.6 million tablets of HCPs from a truck stop in Troy, Illinois. A total of 16,660,400 dosage units of HCPs were stolen. The tractor and trailer were recovered separately, with the cargo found almost intact.

In August 2007, DEA Diversion Investigators traveled to Chicago, Illinois, to speak with a DEA registrant (MD) in regards to excessive ordering of HCPs (Vicodin) in various strengths. In an eighteen month period (January 2006 – June 2007) the registrant ordered 3,498,276 dosage units of HCPs. 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 HCPs and 3,388 tablets of alprazolam. A federal grand jury returned a three count indictment against the suspect for possession of HCPs and alprazolam and conspiracy to distribute HCPs.

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 HCPs 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 HCPs tablets were found in their vehicle.

Beginning March 2006, DEA received information regarding the illicit prescribing of HCPs 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 HCPs 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 HCPs.

In December 2007, a Houston based Pharmacist was charged as financier and leader of an interstate trafficking group which distributed large quantities of HCPs 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 HCPs.

In September 2007, culminating a yearlong 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 HCPs.

In January 2008, a 54 count indictment against the Physician Operator of a pain clinic was issued for prescribing millions of dosage units of HCPs 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.

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 HCPs and OxyContin® prescriptions. The unlawful prescribing from these clinics has resulted in at least seven documented deaths in the Pensacola area.

In March 2008, three pharmacies in San Diego, CA, all owned by a single pharmacist, were involved in the diversion of large amounts of HCPs (including Vicodin) and oxycodone product. In one pharmacy, over 90,000 HCPs tablets were distributed illegally and in another, 5,449 HCPs
tablets were diverted in a single month. DEA’s STRIDE system reports that 13,396 HCPs tablets were seized in this investigation.

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 HCPs, and filled prescriptions without identification. A March 2007 audit revealed shortages of 47,081 dosage units for HCPs, APAP with codeine and alprazolam.

In February, 2008, a pharmacy technician employed at an independent pharmacy in Red Bluff, California, who also worked as a delivery driver for a pharmaceutical distributor in Redding, was arrested with two accomplices for diverting HCPs, Morphine, and OxyContin. During the 11-month investigation, 2,500 HCPs, 55 Morphine, and 318 OxyContin tablets were purchased in five undercover transactions. The pharmacy technician was convicted and sentenced to 25 months imprisonment.

In February, 2008, a psychiatrist employed in private practice in Riverside, California was arrested for unlawfully distributing HCPs, Oxycodone product, and other Schedule II and III Controlled Substances. The investigation revealed that the psychiatrist from 2005 to 2007 wrote prescriptions for more than 68,000 doses of HCPs, 37,000 doses of Xanax, and thousands of doses of Schedule II Controlled Substances. The psychiatrist was sentenced to 10 years imprisonment followed by three years supervised release.

In May, 2009, a physician employed in private practice in San Fernando, California was found guilty of 13 felony counts of writing unlawful prescriptions for HCPs, Oxycodone product, and Xanax outside the usual course of medical practice and without a legitimate medical purpose. During the trial, the physician admitted to making $30,000 per week in cash payments for the prescriptions he wrote. The physician was sentenced to 25 years imprisonment followed by six years supervised release and fined $1,000,000.

Per DEA press release issued June 6, 2010, a criminal complaint was filed against a dentist for conspiracy to distribute HCPs. A police confidential source provided information that the dentist was supplying them with 500 to 1,000 HCPs tablets a week from his office and from his home. During the investigation the confidential source purchased a total of 3500 HCPs tablets for $4,550 and the transactions were observed and/or recorded.

In May, 2011, a physician employed in private practice in Portsmouth and Chillicothe, Ohio was convicted of 18 counts of illegal drug distribution, including four counts of distribution resulting in death. The physician prescribed and dispensed millions of dosages of various drugs, including HCPs, Oxycodone product, Alprazolam, and Diazepam out of three clinic locations. The
physician’s clinics opened their own on-site dispensaries after local pharmacies refused to fill prescriptions written by the physician. The physician received life sentences for each of the four counts of distribution resulting in death and was ordered to forfeit $1,200,000.

An employee of a Skokie, IL pharmacy was arrested for illegally selling an estimated 700,000 HCPs tablets, with an estimated street value of $7 million.

Per DEA press release issued March 22, 2011, a Lewiston, Idaho pharmacist was sentenced after admitting to the theft of 200 to 300 HCPs tablets from the pharmacy in which he was employed.

Per DEA press release issued June 4, 2011, a pharmacy owner and pharmacist who operated pharmacies in Riverside and Los Angeles Counties was sentenced to federal prison for illegally dispensing approximately 2 million dosage units of HCPs.

In April, 2012, an owner of three pain clinics in central and southern Ohio and six doctors employed in those clinics were indicted for illegal drug distribution. The investigation revealed that the three clinics served customers who traveled hundreds of miles from throughout Ohio, Kentucky, West Virginia, and Tennessee based on cash payments of $200 per office visit for prescriptions of HCPs, Oxycodone product, Diazepam, and Alprazolam with little or no physical examination. Two of the six doctors were charged with distribution of controlled substances resulting in death.

Per DEA press release issued October 4, 2011, four former pharmacy technicians were arrested and charged with the alleged theft of prescription drugs (including HCPs) from retail pharmacies where they worked.

Per DEA press release issued October 4, 2012, a pharmacist working in a family owned pharmacy was found guilty of three counts of dispensing HCPs, oxycodone product and alprazolam without valid prescriptions.

Per DEA press release issued November 15, 2012, a federal jury convicted three people of crimes related to a multi-state conspiracy that sent millions of dollars’ worth of highly addictive prescription painkillers (including HCPs) to all 50 states.

A licensed medical assistant working for a cardiologist used the doctor’s DEA registration number to call in fraudulent prescription for HCPs using the names of actual patients. Approximately 97,000 tablets were distributed by 89 pharmacies under the falsified authority of the doctor.
Per DEA press release issued January 29, 2013, a Philadelphia physician was sentenced to seven years in prison for conspiracy to distribute controlled substances and 17 counts of distribution of controlled substances via a pill mill run out of his office. The physician was distributing HCPs, oxycodone product and alprazolam to cash paying customers, without any medical examinations. The physician later created phony medical records for his drug-buying customers.

Per DEA press release issued March 12, 2013, an individual plead guilty to one count of conspiracy to distribute and possess with intent to distribute a controlled substance. According to court documents the individual obtained the prescription drugs through multiple prescriptions from physicians and from other unidentified sources. At the time of arrest, the individual was in possession of 10,000 HCPs dosage units, 12,000 oxycodone product dosage units and 29,000 alprazolam dosage units.

Per DEA press release issued March 19, 2013, thirteen individuals, including five doctors, four pharmacists and a home health agency owner, were charged with participating in a large scale health care fraud and drug distribution scheme, through 26 pharmacies statewide. The controlled substances involved were HCPs, oxycodone product, alprazolam and codeine cough syrup.

Per DEA press release issued May 13, 2013, a West Hollywood physician was indicted for allegedly writing over 1200 HCPs prescriptions after a federal order had revoked his DEA registration/authority to prescribe controlled substances.

Per DEA press release issued August 19, 2013, an Indianapolis physician was charged with 24 felonies for allegedly writing prescriptions for HCPs, methadone and oxycodone product without legitimate medical purpose, outside the usual course of professional practice or without a license.

Per DEA press release issued September 19, 2013, thirty-three individuals were arrested and charged with fraudulently obtaining HCPs, oxycodone product and alprazolam by calling in fraudulent prescriptions, utilizing stolen prescriptions, altering prescriptions and/or “doctor shopping”. The investigation uncovered over 300 prescriptions and 32,000 dosage units of controlled substances.

Per DEA press release issued October 18, 2013, a Healthcare Center Nursing Supervisor was arrested and charged with selling unused prescription drugs that included HCPs, alprazolam and fentanyl for a profit of over $60,000 in a one year period.