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January 16, 2013

The Honorable Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Dear Commissioner Hamburg:

Attached is a courtesy copy of a letter that we have sent to the members of your Drug Safety and Risk Management Advisory Committee that will be meeting on January 24th and 25th to review the rescheduling of hydrocodone combination products from Schedule III to Schedule II of the Controlled Substances Act.

The nonmedical use of opioids, according to the White House Office of National Drug Control Policy, has reached epidemic levels in the United States and causes about 15,000 deaths each year. No one can say for certain how many of these victims were patients or former patients at the time of their death but experts have suggested that a sizable number of them may have commenced their final journey as legitimate pain patients seeking relief from oxycodone or hydrocodone drugs prescribed for them.

In recommending the rescheduling of hydrocodone products we are not in any way advocating restricting patient access to this important medicine. Rescheduling, however, would tighten the security in the handling of hydrocodone products, improve the accountability of prescribers and dispensers, and safeguard the interests of patients whose treatment and recovery would entail closer medical supervision. Rescheduling may not be the ideal solution or the only solution, but we believe that it would be an important first step in protecting the nation's public health by helping to reduce the mortality and morbidity associated with the excessive use and misuse of Schedule III hydrocodone combination products.

Sincerely,

Robert L. DuPont, M.D.
Former Director, NIDA

Peter B. Bensinger
Former Administrator, DEA

John J. Coleman, Ph.D.
Retired Ass't Administrator, DEA

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[To each member of the FDA Drug Safety and Risk Management Advisory Committee]

Dear _____:

On January 24 and 25, 2013, the Food and Drug Administration's (FDA) Drug Safety and Risk Management Advisory Committee will meet to consider rescheduling hydrocodone combination products from Schedule III to Schedule II of the Controlled Substances Act (CSA). By this letter, we respectfully offer our views on this matter to you and the other members of the Advisory Committee. Our views are based on many decades of work in public health policy and drug abuse prevention.

In 1969, when Congress was considering passage of the CSA, there was opposition from the medical community to a provision that would give drug-scheduling authority exclusively to the Attorney General. Even within government, there was opposition to this. Almost 100 doctors and scientists of the then-Department of Health, Education, and Welfare (HEW), the predecessor agency to today's Department of Health and Human Services (DHHS), signed a letter to Congress opposing their Secretary's support for this portion of the bill.[1]

To resolve the controversy, drug scheduling responsibility was bifurcated. The new Act gave the Attorney General rulemaking authority to schedule drugs, but only upon a binding recommendation and a medical and scientific evaluation from the Secretary. To facilitate the process of scheduling drugs, rescheduling drugs, or removing drugs entirely from the schedules, the Act permitted the Attorney General to initiate such action on his or her own motion, pursuant to a request of the Secretary, or "on the petition of any interested party."[2]

In 1999, acting as an "interested party," Ronald J. Dougherty, M.D., FAAP, ASAM, an addiction medicine specialist and director of a drug treatment center in New York, filed a petition with the Drug Enforcement Administration (DEA) in which he requested that all hydrocodone

[1] See Schmeck HM. H.E.W. Scientists Score Drug Bill: 100 Sign a Letter Criticizing Administration Proposal. The New York Times. May 2, 1970.
[2] See 21 USC 811(a).

combination products be rescheduled from C-III to C-II of the CSA.[3] Dr. Dougherty provided grounds for his request gathered from over three decades of clinical practice, as well as from various government publications.[4]

Five years later, in July 2004, DEA sent Dr. Dougherty's petition to the DHHS for a rescheduling recommendation and a medical and scientific evaluation. In March 2008, four years later and nine years after Dr. Dougherty filed his petition with DEA, DHHS responded with a recommendation to maintain hydrocodone combination products in Schedule III.[5]

In February 2009, the DEA renewed its request to DHHS and supplied additional information. Since then, at least two bills were introduced in Congress to reschedule hydrocodone products. Although the bills failed, Congress expressed its continued interest in the matter by including in last summer's enactment of the Food and Drug Administration Innovation Safety Act a provision requiring that the FDA convene a meeting "to solicit advice and recommendations to assist in conducting a scientific and medical evaluation" on whether to reschedule combination drug products containing hydrocodone.[6] The Advisory Committee meeting scheduled for later this month is being held pursuant to this provision in the Act.

That it has taken 14 years and an Act of Congress to get Dr. Dougherty's petition before your Advisory Committee hardly speaks well for the Government's ability to decide such issues. With respect to the question of whether hydrocodone products should be rescheduled from C-III to C-II, we believe that the briefing materials furnished by the FDA in anticipation of your meeting show that the DEA has made a compelling case for rescheduling by using, in part, data published by DHHS agencies. We have reviewed these data and conducted our own analyses that we will describe in more detail below.

The Substance Abuse and Mental Health Services Administration, an agency of the DHHS, manages the Drug Abuse Warning Network, a public health surveillance system that collects information about the abuse and misuse of drugs, including pharmaceutical drugs, reported by hospital emergency departments. These data are extrapolated to estimate annual national drug abuse frequencies and trends.

The Automation of Records and Consolidated Orders System (ARCOS) is managed by the DEA and tracks the lawful distribution of certain drugs, including C-II and C-III opioids, sold to hospitals, pharmacies, and practitioners. By law, drug manufacturers and distributors of controlled substances are required to report their transactions to DEA on a timely basis. ARCOS provides a precise measurement of the distribution of opioids used for medical purposes.

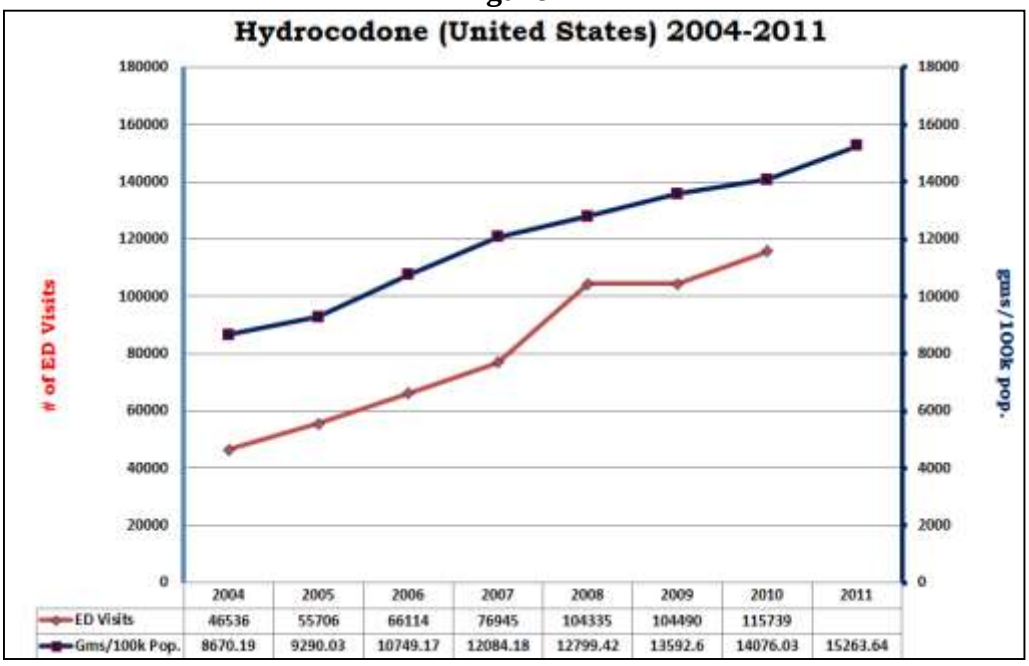
A third component comes from research by epidemiologists of the Centers for Disease Control and Prevention (CDC) that suggests a close linear relationship over time between the prescribing

[3] By regulation, citizens' petitions for rulemaking actions to schedule, reschedule or remove a drug from the schedules, must be submitted to the DEA. See 21 CFR 1308.43.
[4] See FDA Briefing Materials, p. 45.
[5] Id.
[6] See 77 Fed. Reg. 34,051 (June 8, 2012); FDASIA, Pub. L. No. 112-144, 126 Stat. 993, § 1139(a) (2012).

of opioids and their involvement in unintentional overdose deaths.[7] This body of research demonstrates that as the prescribing of opioids for medical purposes increases, the number opioid-related overdose deaths increases proportionally.

In our first example (Fig. 1), we show that by using ARCOS data as our numerator and frequency of hydrocodone mentions in hospital admissions for drug-related emergencies as our denominator, a close linear relationship exists over time between the amount of hydrocodone prescribed in grams per 100k population and the frequency of hydrocodone mentions in hospital emergency department admissions.[8]

Figure 1



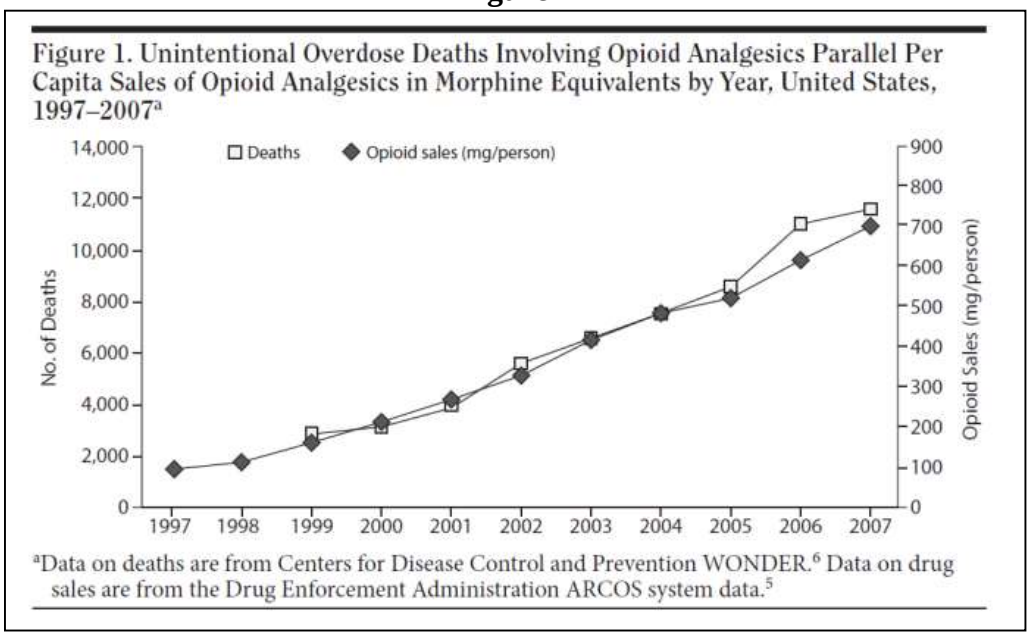
Our second example (Fig. 2) shows CDC data that indicate a similar statistical relationship between the increased "sales (mg/person)" of opioids (shown collectively as morphine equivalents) and unintentional overdose deaths involving opioids. Paulozzi and colleagues (2011) graphed these data over an 11-year period, showing a near perfect linear relationship.[9]

[7] See Paulozzi LJ, Weisler RH, Patkar AA. A national epidemic of unintentional prescription opioid overdose deaths: how physicians can help control it. J Clin Psychiatry. Apr 19 2011;72(5):589-592. See also Paulozzi LJ, Kilbourne EM, Shah NG, et al. A History of Being Prescribed Controlled Substances and Risk of Drug Overdose Death. Pain Med. Oct 25 2011.

[8] Sources: DEA ARCOS, published 2004-2006, unpublished 2007-2011 (obtained by author via FOIA, August 2012); ED visits: DHHS, Substance Abuse and Mental Health Services Administration, DAWN, 2004-2010, "all misuse and abuse."

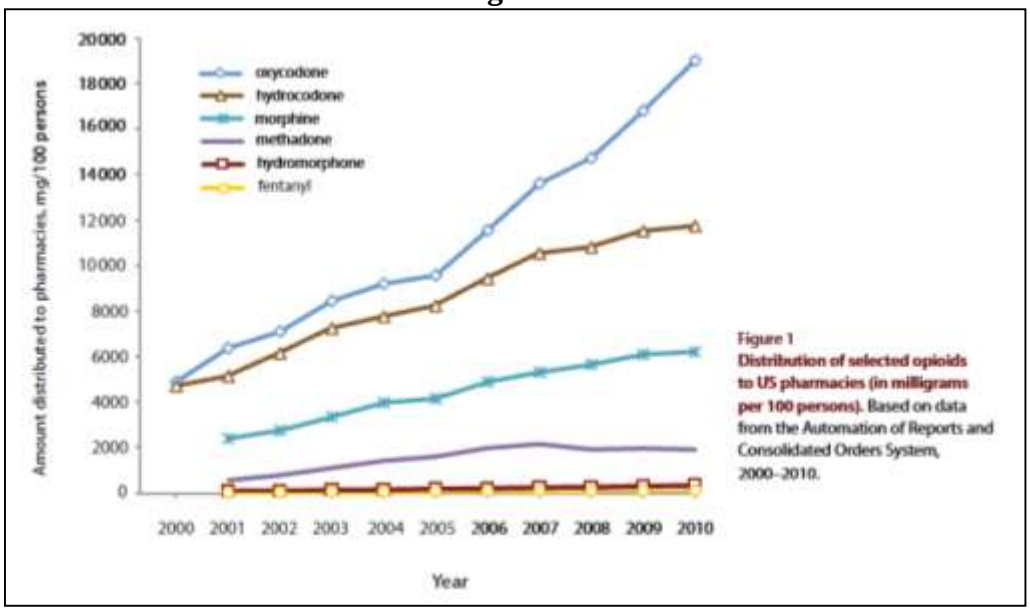
[9] See Paulozzi LJ, Weisler RH, Patkar AA. A national epidemic of unintentional prescription opioid overdose deaths: how physicians can help control it. J Clin Psychiatry. Apr 19 2011;72(5):589-592.

Figure 2



Our third example (Fig. 3) comes from Kenan and colleagues (2012) who tracked the distribution of six popular opioids to pharmacies in the U.S. over an 11-year period ending in 2010. Using ARCOS data to show milligrams per 100 persons, the Kenan team found a sharp increase in the volume of hydrocodone distributed over this period.[10]

Figure 3



[10] See Kenan K, Mack K, Paulozzi L. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000–2010. Open Medicine. 2012;6(2e41).

It is our belief that the above research supports rescheduling hydrocodone products from C-III to C-II. We share this belief with several thousand addiction medicine specialists and members of the American Society of Addiction Medicine (ASAM). In a letter dated November 6, 2012, to FDA Commissioner Margaret A. Hamburg, M.D., the acting President of ASAM stated:

> "It has been over 40 years since hydrocodone was originally classified as a Schedule III drug, per the Controlled Substances Act (CSA). At that time, neither the abuse liability nor the potency of hydrocodone were well understood. Today, we know that this drug is both potent and highly addictive. Unfortunately, the CSA still misclassifies hydrocodone as a drug with a potency that is six times weaker than that of oral morphine when, in fact, hydrocodone and morphine have the same potency (e.g., a 10mg dose of oral hydrocodone produces the same effects as a 10mg dose of oral morphine.) This misclassification also misrepresents the addiction potential of this drug. There is widespread agreement that hydrocodone has the same abuse liability as oxycodone and other Schedule II opioids.
>
> The United States is currently facing its worst drug epidemic in 40 years, according to the CDC. Drug overdose deaths now exceed the number of overdose deaths from the heroin epidemic of the 1970s and the crack cocaine epidemic of the 1980s, combined. Updating the classification of hydrocodone in the CSA would be one of the single most important interventions the federal government could implement to bring this raging epidemic under control."[11]

During the upcoming Advisory Committee meeting, you may hear from witnesses who will claim that rescheduling hydrocodone analgesic products will diminish patient access to this important class of drugs. In defending the present status of these products, some may cite the convenience of allowing prescribers to "call in" prescriptions for C-III hydrocodone combination products. Unlike prescriptions for C-II drugs, prescriptions for C-III, C-IV and C-V drugs may be telephoned or sent by facsimile to a patient's pharmacy and refills may be authorized by the prescribing authority up to five times within six months.[12] While these no doubt are conveniences for legitimate patients as well as their physicians, they come at an enormous and unacceptable cost to the nation's public health.

In the briefing materials provided by the FDA are copies of the DEA rescheduling requests sent to DHHS over the years since 2004. Included are actual accounts taken from case files that show why the C-III classification of hydrocodone products has figured prominently in its diversion from hospital and pharmacy supplies. Because a signed prescription is not needed to obtain or dispense C-III controlled substances, hydrocodone products often are unlawfully obtained by fraud. Moreover, pharmacists report that because they are such popular drugs, large bottles of hydrocodone combination products may be left unguarded on pharmacy shelves where they become easy targets for in-house thieves. By comparison and with very few exceptions, C-II drugs may be dispensed only pursuant to a signed written prescription, and C-II drugs must be

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[11] See Letter, dated November 6, 2012, from Acting President Stuart Gitlow, MD, MBA, MPH, FAPA, American Association of Addiction Medicine to FDA Commissioner Margaret A, Hamburg, M.D. (available: http://www.asam.org/docs/asam-news-archives/fda-rescheduling-hydrocodone-comments.pdf)

[12] See 21 CFR 1306.22.

secured by the pharmacy in a locked safe or steel cabinet where limited access prevents their diversion.[13]

During the meeting, you also may hear presentations suggesting that, compared with most C-II opioids, hydrocodone products have a lower abuse potential, as measured by a ratio of hospital emergency department mentions to total prescriptions dispensed. This commonly used metric may not be an accurate abuse indicator in this instance because the number of prescriptions dispensed for hydrocodone products each year is greater than the total for all other opioids combined. Presumably, because most hydrocodone prescriptions are issued for legitimate medical purposes, the ratio of misuse and abuse mentions, as measured by hospital emergency department mentions to total prescriptions dispensed, will be diluted when making comparisons with individual C-II opioids for which far fewer prescriptions are dispensed. Differences noted in the ratios calculated for hydrocodone products and C-II opioids may reflect sample size variances rather than actual abuse potential.

The CSA prohibits the refilling of C-II prescriptions because of their high abuse potential and the need for close medical supervision in their prescribing.[14] In 2010, according to DHHS, there were 182,748 cases of "misuse and abuse" of oxycodone reported by hospital emergency departments. This was the highest number of such mentions for any opioid. Second place, with 115,739 mentions, went to hydrocodone combination products. In 2010, prescriptions for hydrocodone products represented two-thirds of all prescriptions for the top six opioids.[15]

When it comes to regulating abusable drugs, experts emphasize the need for greater vigilance in protecting children, especially adolescents who may be tempted to experiment with controlled substances. Hydrocodone combination products must be considered in the context of medicinal drugs that pose alarmingly high risks for young people, possibly because hydrocodone combination products are so frequently prescribed and, as a result, are likely to be present in many family medicine cabinets.

On the specific topic of teenagers abusing opioids, Nora Volkow, M.D., Director of the National Institute on Drug Abuse (NIDA) has reported:

> "(S)ince 2002, the US prevalence of high school seniors reporting past-year nonmedical use of opioids has been 8% to 10% for hydrocodone and 4% to 5% for oxycodone. After

[13] See 21 CFR 1301.72.

[14] See 21 CFR 1306.12; Note: On December 19, 2007, DEA issued a Final Rule allowing "practitioners to provide individual patients with multiple prescriptions, to be filled sequentially, for the same schedule II controlled substance, with such multiple prescriptions having the combined effect of allowing a patient to receive over time up to a 90-day supply of that controlled substance." See FR Doc E7-22558 [Federal Register: November 19, 2007 (Volume 72, Number 222)] [Rules and Regulations] [Pages 64921-64930].

[15] Number and (%) of top six opioids prescribed in 2010: Oxycodone: 48,227,000 TRx (26%); methadone: 4,559,000 TRx (2.5%); morphine/combinations: 2,740,000 TRx (1.5%); fentanyl: 4,915,000 TRx (2.6%); hydromorphone/combinations: 2,276,000 TRx (1.2%). By comparison, C-III hydrocodone products: 122,807,000 TRx (66.2%). Total TRx for all these opioids in 2010 estimated as 185,520, 000 --according to industry sources (www.DrugTopics.com).

> excluding alcohol and tobacco, the prevalence of hydrocodone abuse is second only to marijuana abuse."[16]

Reports from NIDA also show that, as measured by emergency department records between 2004 and 2009, increases in hydrocodone abuse ranked third among pharmaceuticals and even exceeded rates noted for illicit drugs:

> "The largest pharmaceutical increases [i.e., between 2004 and 2009] were observed for oxycodone products (242.2 percent increase), alprazolam (148.3 percent increase), and hydrocodone products (124.5 percent). Among ED visits involving illicit drugs, only those involving ecstasy increased more than 100 percent from 2004 to 2009 (123.2 percent increase)."[17]

Of interest in regard to this NIDA reference is that all oxycodone products, both single entity and combination drugs, are C-II controlled substances, alprazolam is a C-IV controlled substance, and all hydrocodone combination products are C-III controlled substances. As previously noted, this raises once again a question about the validity of using only emergency department data as a basis for drug classifications.

Finally, during your meeting you will hear from many presenters, including representatives of DHHS, FDA, medical organizations, and private citizens. Also on the agenda is a presentation by the Generic Pharmaceutical Association (GPhA), a lobbying organization that, according to congressional records filed pursuant to the Lobbying Disclosure Act of 1995, expended $504,925.00 in lobbying expenses during the second quarter of 2012. This sum included lobbying expenses incurred in relation to the aforementioned Act that requires the FDA to convene the meeting that you will be attending at the end of this month.[18]

One organization, however, that you will not be hearing from during your two-day meeting will be the DEA, the agency that took up the campaign to reschedule hydrocodone products almost a decade ago and today remains in the forefront of this important public health and public safety effort. No explanation has been given by the FDA for why the DEA was excluded from this important meeting.

In your deliberations, we ask that you consider the information we have provided here, information that we believe is both compelling and important in making the case for rescheduling hydrocodone combination products from C-III to C-II. We agree with the experts who say it would be an important first step in reducing the epidemic of opioid abuse and diversion that is taking a severe toll on our nation. We believe that it would be far more effective than other risk management strategies currently in place to reduce opioid abuse. In this regard, it is worth noting that our nation's prescription drug abuse problem involves just a handful of

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[16] See Volkow N. Curtailing Diversion and Abuse of Opioid Analgesics Without Jeopardizing Pain Treatment. JAMA. 2011;305(13).

[17] See National Institute on Drug Abuse. DrugFacts: Drug-Related Hospital Emergency Room Visits. 2011; http://www.drugabuse.gov/publications/drugfacts/drug-related-hospital-emergency-room-visits. Accessed Jan 14, 2013.

[18] See http://soprweb.senate.gov/index.cfm?event=getFilingDetails&filingID=464ADFD4-5853-4BE0-9236-3E2889FEAAA8

widely used opioid products. There is no mistaking that hydrocodone ranks high among the drugs on this list.

Remarkably, the United States consumes almost 99 percent of all the hydrocodone in the world.[19] In 1999, when Dr. Dougherty filed his petition, the amount hydrocodone used for medical purposes in the U.S. per 100k population was 4,357.03 grams. By 2011, this figure had increased 250.3 percent, to 15,263.64 grams per 100k population.[20] Neither population growth nor a change in the prevalence or treatment of pain justifies this enormous increase.

The market for hydrocodone analgesics generates $2 billion dollars a year in revenue. These vital medicines are made and distributed by at least 21 companies, large and small, with each having a major stake in the marketing of its hydrocodone products. Rescheduling hydrocodone analgesic products from C-III to C-II may reduce sales of these drugs, but legitimate patients who need and rely on them will still be able to obtain them, albeit under closer supervision by prescribing authorities. In addition, rescheduling would enhance the security of hydrocodone combination products along the supply chain and at hospitals and pharmacies.

Based on the above and experiences gained from our many years of public and private service in the field of health policy and drug abuse prevention, we conclude that the rescheduling of hydrocodone combination products from C-III to C-II is fully justified at this time. In addition, we believe that rescheduling will significantly improve the overall health and safety of the American public by reducing the mortality and morbidity currently associated with the widespread diversion and abuse of hydrocodone combination products. We urge you to consider the information in this letter when you meet in session with the FDA later this month.

Thank you for your interest in this issue and for your service on the FDA's Advisory Committee.

Sincerely,

Robert L. DuPont, M.D., Former Director, National Institute on Drug Abuse (1973-1978); Fellow, American Society of Addiction Medicine

Peter B. Bensinger, Former Administrator, Drug Enforcement Administration (1976-1981)

John J. Coleman, Ph.D., Retired Special Agent and former Assistant Administrator for Operations, Drug Enforcement Administration (1965-1998); President, Drug Watch International, Inc. (www.drugwatch.org)

[19] See Kuehn B. Opioid Prescriptions Soar. *JAMA*. 2007;297(3):249-253.
[20] DEA ARCOS published data (http://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/1999/index.html) and unpublished data for 2011 obtained by author via FOIA in August 2012.