PROP
PHYSICIANS FOR RESPONSIBLE OPIOID PRESCRIBING

VIA ELECTRONIC SUBMISSION: http://www.regulations.gov

November 6, 2012

Margaret A. Hamburg, MD
Commissioner of Food and Drugs
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2012-N-0548

Dear Commissioner Hamburg:

Physicians for Responsible Opioid Prescribing (PROP), an organization with a mission to reduce morbidity and mortality caused by overprescribing of opioids, is pleased to submit a comment on Docket No. FDA-2012-N-0548, as the Drug Safety and Risk Management Advisory Committee considers a schedule change for hydrocodone combination products (HCs). PROP's members include clinicians and researchers in the fields of Pain, Addiction, Public Health, Emergency Medicine, Internal Medicine, Primary Care, Occupational Medicine, Evidence-Based Medicine and other specialties.

We believe that the Food and Drug Administration (FDA) mishandled the request by the Drug Enforcement Administration (DEA) to reschedule HCs. Had FDA responded in a timely and appropriate manner to DEA's urgent request, thousands of overdose deaths and tens of thousands of cases of opioid addiction might have been prevented.

In 2004, DEA sent FDA a thorough analysis of the abuse and addiction potential of HCs and asked FDA to follow procedures outlined in the Controlled Substance Act that would make it possible to change HCs to schedule II. In DEA's memo to FDA, the following findings were highlighted:

- Human and animal studies indicate that hydrocodone is equipotent to morphine, has an abuse liability similar to morphine and produces effects that are indistinguishable from morphine.
- HCs are associated with significant diversion and are "the most frequently encountered opiate pharmaceutical in forensic laboratory submissions of drug evidence."
- HC's are among "the most widely abused" pharmaceuticals in the United States.
- No data can be found to support keeping HC's in the less restrictive Schedule III category.

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In 2004, when FDA received this request from DEA, trends indicating a sharp increase in rates of opioid analgesic addiction and overdose deaths associated with increased opioid prescribing were already apparent. Despite the urgency of DEA's request, FDA waited four years to respond by issuing a denial.

FDA's denial was explained in a memo entitled "Basis for the Recommendation to Maintain Hydrocodone Combination Products in Schedule III." This deeply flawed report came to the astonishing conclusion that patients are incapable of becoming addicted to HCs. According to the FDA's report:

> *In conclusion, it is expected that patients using hydrocodone products therapeutically for the management of chronic pain, depending on the length exposure and dose taken, may develop moderate or low physical dependence, but not addiction, which implies impaired control over drug use, compulsive use of the drug.*

Background

When the Controlled Substances Act (CSA) was passed into law 42 years ago, one of its primary purposes was to place drugs with similar abuse liability into distinct categories called *schedules*. This sensible approach to categorizing narcotics made it possible to link regulations to a drug's schedule, allowing for easier access to drugs with less risk, while maintaining greater restrictions on riskier drugs. In addition, the scheduling of drugs created a mechanism for informing the medical community and the public about how addictive a particular drug might be.

There is, however, an important rule that must be followed for the scheduling of drugs to have the effect the CSA intended. Drugs with similar abuse liability and addiction potential must be placed into the same schedule. If drugs are incorrectly scheduled, the system falls apart. For example, if a highly-addictive drug is incorrectly placed in a category intended for drugs with lower abuse liability, then prescribers, patients and even teenagers curious about experimenting with the drug, might underestimate risks. In addition, the ability to reduce inappropriate availability of the drug in classrooms, college dormitories and on the black market will be hindered. This is exactly what has been happening with HCs.

In 1970, when the CSA was drafted, HCs were incorrectly scheduled. At the time, hydrocodone's pharmacologic properties were not well understood. Evidence of this can be found by comparing the amount of hydrocodone permissible in a Schedule III combination product to the amount of morphine that is permitted in a Schedule III combination product. Whereas the CSA's Schedule III category permits up to 15mg of hydrocodone in a pill containing 325 mg of acetaminophen (APAP), it only allows up to 0.16mg of morphine in combination with 325mg of APAP. This suggests that when the CSA was written, morphine was believed to have a far higher potency than hydrocodone. We know today that the potency of oral hydrocodone is equal to the potency of oral morphine. This error in the CSA explains why Vicodin (hydrocodone-APAP) is Schedule III and Percocet (oxycodone-APAP) is Schedule II, even though Vicodin and Percocet have a similar abuse liability.[1]

Why HCs belong in Schedule II

The CSA's criteria for Schedule II are listed below:

Schedule II:

1. The drug or other substance has a high potential for abuse.
2. The drug or other substance has a currently accepted medical use in treatment in the United States, or a currently accepted medical use with severe restrictions.
3. Abuse of the drug or other substances may lead to severe psychological or physical dependence.

According to these criteria, HCs should be categorized as Schedule II because they have a high potential for abuse and because use can lead to addiction. The DEA presented the FDA with an abundance of human and animal studies, as well as epidemiological data, indicating that HCs are addictive and have a high potential for abuse.

Morphine, hydrocodone and oxycodone all have similar molecular structures and interact in a similar fashion with the brain's mu-opioid receptor. See Figure 1.

Figure 1

Based on these similarities, one would predict that morphine, hydrocodone and oxycodone would have similar abuse and addiction potential. Multiple in-vivo studies comparing equivalent doses of hydrocodone, oxycodone and morphine have confirmed that they all produce similar effects. Conclusions from three recent studies comparing hydrocodone to oxycodone and morphine are listed below:

> Zacny JP and Gutierrez S. 2009:[1] "Consistent with a recent study published in this journal using identical doses of hydrocodone and oxycodone (without APAP) in prescription opioid abusers, we found little difference in the pharmacodynamic effects of hydrocodone-APAP and oxycodone-APAP in non-drug-abusing volunteers."

Walsh SL, et al. 2008:[2] "These data suggest that the abuse liability profile and relative potency of these three [oxycodone, hydrocodone and oxymorphone] commonly used opioids do not differ substantially from one another and suggest that analgesic potencies may not accurately reflect relative differences in abuse liability of prescription opioids."

Stoops WW, et al. 2010:[3] "There were modest potency differences between oxycodone, hydrocodone, and morphine, but their overall profile of effects was similar, indicating significant abuse potential when administered intravenously."

Indicators of Hydrocodone Abuse

Evidence that the abuse potential of hydrocodone-combination products is similar to the abuse potential of Schedule II opioids goes well beyond the laboratory setting. Multiple population-level indicators provide strong evidence that hydrocodone's abuse liability is equivalent to oxycodone and other opioids.

Commonly used indicators of a drug's abuse liability include the following data sets:

1) Emergency room visits for non-medical use (SAMHSA).
2) The National Drug Use Survey (SAMHSA).
3) Calls to Poison Control Centers (RADARS).
4) Survey data from patients receiving addiction treatment (RADARS).
5) Survey data from "Key Informants" (RADARS).
6) Drug Diversion data from criminal justice agencies (RADARS).
7) Surveys of college students (RADARS).

On five of these seven indicators, HCs are ranked above all other opioids. Hydrocodone-combination products are ranked second for the remaining two indicators. Please see Figure 2, Figure 3 and Figure 4.

Figure 2

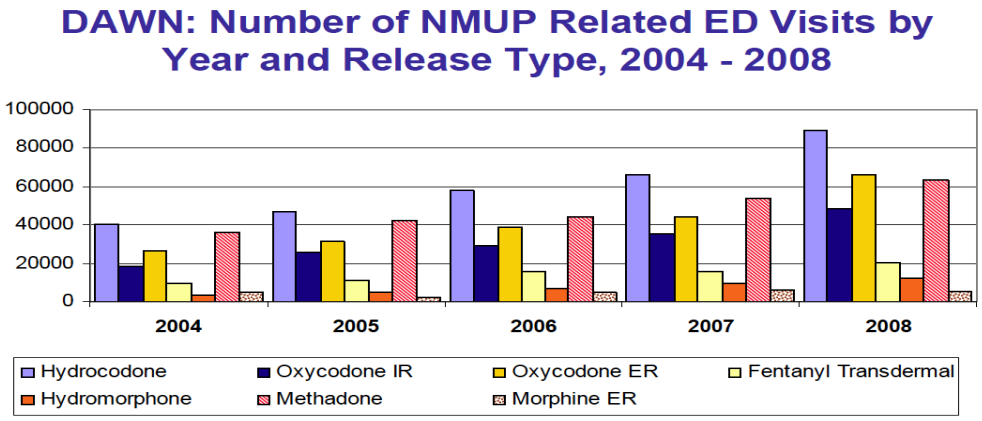

Figure 3. Trends in Nonmedical Use of Oxycodone and Hydrocodone Products among Persons Aged 12 or Older Who Used Pain Relievers Non-medically for the First Time in the Past Year: Numbers in Thousands, 2002-2010. Source: SAMSHA

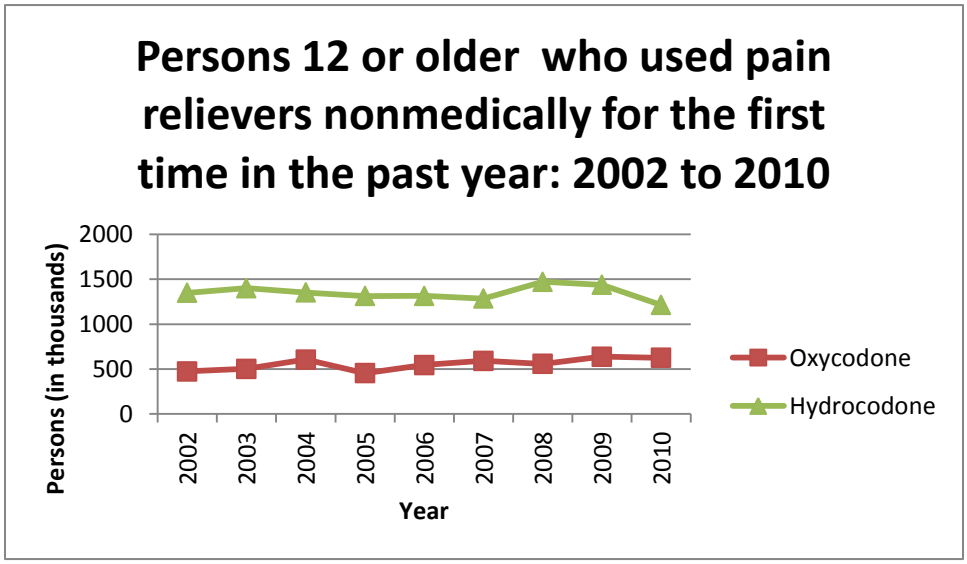

Figure 4. RADARS System Opioid Abuse Trends-Population Rate (Ranked Highest-Lowest) 2011

Source: Richard Dart, MD, PhD; RADARS Sixth Annual Meeting. April 24, 2012

Rank	Poison Center	Opioid Treatment	Survey of Key Informant Pts	Drug Diversion	College Survey
1	Hydrocodone	Oxycodone	Hydrocodone	Oxycodone	Hydrocodone
2	Oxycodone	Hydrocodone	Oxycodone	Hydrocodone	Oxycodone
3	Tramadol	Methadone	Morphine	Morphine	Morphine
4	Methadone	Morphine	Hydromorphone	Buprenorphine	Tramadol
5	Morphine	Hydromorphone	Methadone	Methadone	Fentanyl
6	Buprenorphine	Buprenorphine	Buprenorphine	Hydromorphone	Methadone
7	Fentanyl	Fentanyl	Fentanyl	Tramadol	Buprenorphine
8	Hydromorphone	Tramadol	Tramadol	Fentanyl	Hydromorphone

Concerns about Unintended Consequences

Several special interest groups have been lobbying against rescheduling HCs. These groups successfully blocked an amendment to the Prescription Drug User Fee Act re-authorization legislation that would have corrected the error in the CSA by placing HCs into Schedule II. These groups have argued that the schedule change would result in a burden for pharmacists, patients and prescribers.

While some of these concerns about increased burden may be legitimate, a phase-in period for up-scheduling of HCs would provide an opportunity to minimize unintended consequences. It is also important to note that the CSA does not give FDA the authority to maintain HCs in the incorrect schedule because of concerns about unintended consequences. The CSA requires scheduling on the basis of a drug's inherent characteristics. The law does not permit us to keep a highly-addictive drug in the wrong category because pharmacists, prescribers and patients have gotten used to it being there.

Conclusion

Keeping a loophole in place so that a strong narcotic can remain more easily available is inappropriate and is a violation of the CSA. The only way that the CSA can protect the public from overexposure to highly-addictive medicines is if we correctly categorize them. If we maintain the loophole for HCs, our ability to prevent new cases of opioid addiction that occur among medical and non-medical users of HCs will be hindered and the epidemic of opioid addiction and overdose deaths is likely to continue unabated.

Sincerely,

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Chair, Department of Psychiatry
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References:

1. Zacny JP, Gutierrez S (2009) Within-subject comparison of the psychopharmacological profiles of oral hydrocodone and oxycodone combination products in non-drug-abusing volunteers. Drug Alcohol Depend 101(1–2):107–114.

2. Walsh SL, Nuzzo PA, Lofwall MR, Holtman JR Jr (2008) The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers. Drug Alcohol Depend 98(3):191–202.

3. Stoops WW, Hatton KW, Lofwall MR, Nuzzo PA, Walsh SL (2010) Intravenous oxycodone, hydrocodone, and morphine in recreational opioid users: abuse potential and relative potencies. Psychopharmacology 212(2):193–203.