


DEPARTMENT OF HEALTH & HUMAN SERVICESFood and Drug Administration
Rockville MD 20857

The Honorable Mark E. Souder
Chairman
Subcommittee on Criminal Justice,
Drug Policy and Human Resources
Committee on Government Reform
House of Representatives
Washington, D.C. 20515-6143

APR 26 2004

Dear Mr. Chairman:

Thank you for the letter of March 4, 2004, following up on the testimony of Dr. Robert J. Meyer, Director of the Office of Drug Evaluation II at the Food and Drug Administration's (FDA or the Agency) Center for Drug Evaluation and Research (CDER), delivered on February 9, 2004, before the Subcommittee on Criminal Justice, Drug Policy and Human Resources. Below are your questions followed by our response.

- 1. What legal changes would need to be made to give FDA greater authority to regulate how prescription drugs are prescribed and used after they are given initial approval? What additional changes in the current Federal laws would FDA like to see made? What new steps can Congress take to assist your regulatory efforts to combat the illegal distribution and misuse of prescription drugs?**

The Administration has not determined at this time whether to propose legislation to give FDA greater authority to regulate how prescription drugs are prescribed and used after they are given initial approval. However, FDA would work with Congress if it decided to consider such legislation.

FDA's primary responsibility is to ensure that marketed drugs are safe and effective for their labeled indications. When used correctly, prescription drugs, including opioids, play a very important role in the management of pain and illness. FDA does not regulate the practice of medicine. Medical practitioners can prescribe medications to their patients for on and off-label indications. Primary responsibility in preventing the illegal distribution of prescription drugs resides with State Medical Boards, which license medical practitioners, and State Boards of Pharmacy, which license pharmacists. FDA does, however, take seriously its role in approving drug labels for prescription drugs to ensure that proper instructions and warnings are available to educate the consumer on the correct use of a particular medication. In addition, the Drug Enforcement Agency (DEA) is the primary Federal agency charged with criminal enforcement for drug abuse. FDA recently partnered with DEA and the White House Office of National Drug Control Policy to carry out a coordinated drug strategy to confront the illegal diversion and abuse of prescription drugs. The

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National Drug Control Strategy brings the efforts of FDA, Federal substance abuse prevention and treatment agencies, and law enforcement to bear on the factors contributing to rising prescription drug abuse.

- 2. Does the number of conditions for which a drug is approved by FDA impact the illegal use of the drug? In other words, if the number of approved uses increases, does that increase the potential for the drug to be diverted or misused? Should drugs like OxyContin be approved for use in treating “moderate” or even lesser levels of pain?**

At the September 9 and 10, 2003, Advisory Committee meeting on issues of risk management for the controlled-release opiate drug products, witnesses presented testimony that suggests there is a correlation between how widely a drug is used and the potential for abuse and misuse of that drug.¹ The witnesses suggested that if a drug is very commonly prescribed and commonly used in many settings, it has a higher likelihood of abuse as a result of its wide use. There is not, however, a clear, close relationship between the number of approved uses for a drug and its level of distribution and usage in the community. Drugs with only a single indication may have very widespread use if that single indication is quite common (for example, a new statin drug for hypercholesterolemia may be widely used, due to the prevalence of the condition in the population). On the other hand, a drug that is indicated for treatment of a number of uncommon conditions (for example, rifampin, an antibiotic approved for treatment of tuberculosis and a number of other uncommon infections) may have quite limited usage. Pain is a very common condition in our society, affecting millions of patients, and the extent of use of a drug is driven by many factors beyond indications. The indication for OxyContin is for “the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.” This indication not only bounds the appropriate severity of pain that a patient should have, but also sets other important parameters for the indicated use. For example, OxyContin is not appropriate, by this indication, for “as needed” use nor for short-term use, like after minor trauma or a dental extraction.

FDA approved OxyContin for “moderate to severe” pain rather than just “severe” pain for several reasons. First, pain is not monotonic, and even in patients with chronic painful conditions, their pain tends to wax and wane. Patients with chronic pain may rate their pain as severe one day and only have more moderate levels on another. Further, it is clear from a number of scientific studies that if one looks at significant functional impairment as a threshold for defining significant pain (which is a subjective assessment), many patients with such dysfunction will only rate their pain as moderate or moderately severe, rather than severe. Therefore, patients with pain that importantly limits their daily activities may only rate their pain subjectively as moderate or moderately severe. The question of whether OxyContin and other potent opiates should be limited to severe pain only was posed to the Advisory Committee in the September 2003 meeting. The committee strongly recommended that FDA maintain the indication to include moderate pain. Misuse and abuse of a drug is not driven by FDA’s approved indication. However, legitimate use in practice may be

¹ September 2003 Advisory Committee Transcript -- DEA’s Role in Risk Management of Opiate Analgesics: Terrance Woodworth, M.S.
<http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3978T1.htm>

restricted (when formularies or practice guidelines require following labeled indications), thus negatively affecting the legitimate use of OxyContin.

3. How does FDA determine what the approved dosage or dosages of a prescription drug will be? How does FDA determine what uses will be approved for a drug?

In general, the approved doses for a drug and the approved uses (or indications) are determined by substantial evidence from clinical trials, as called for under the Federal Food, Drug, and Cosmetics Act. For opiates, one needs to determine the lowest effective doses (to help define an appropriate starting dose for the particular drug in question) as well as examine higher doses, since pain intensity and patient's pharmacodynamic responses (that is, responses to a therapy at any given dose) will vary. A further consideration for opiates is that some degree of tolerance is common with chronic use, so that patients may need higher doses over time to maintain satisfactory pain control. Therefore, a range of doses is commonly approved for opiate drug products, such as OxyContin.

As above, the uses or indications for a drug are generally derived from the substantial data provided in clinical trials. For well-established drug classes, including the opiates, prior data from other clinical trials of like or similar drugs and data from the scientific literature may also inform the indications given, so that for a particular drug, the uses approved may not be strictly dictated by the clinical studies done to approve the drug. In the case of products like OxyContin the approved uses were informed both by the clinical studies provided by the sponsor as well as what was otherwise known about the use of opiates in the treatment of chronic pain.

4. On February 15, 2004, the Washington Post reported that "top officials" at the Drug Enforcement Administration were working to reclassify hydrocodone combination products (i.e. drugs that are made up of hydrocodone and another medicine, as opposed to pure hydrocodone) as Schedule II drugs. Would FDA support such a change? Why or why not? Has the abuse of hydrocodone been a significant problem?

As of April 13, 2004, FDA's CDER has not received a petition or an official request from DEA to conduct a medical and scientific recommendation to place hydrocodone combination products under Schedule II of the Controlled Substance Act (CSA). Since we have not seen the petition referred to, the basis for DEA's position is unknown to FDA. The determination to impose additional or more stringent controls upon a particular class of drug products, as publicly proposed by DEA, requires thorough evaluation of the full impact upon patients, the public, the medical community, and manufacturers.

Drug scheduling recommendations are made by the Assistant Secretary of the Department of Health and Human Services (DHHS) after full scientific and medical evaluation of proposed scheduling actions by FDA and DHHS, and often following extensive interagency deliberations and meetings. Hydrocodone is already controlled

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under Schedule II, the most stringent level of control for an approved drug. Only combinations of hydrocodone with acetaminophen or aspirin, containing less than 15 mg of hydrocodone are in Schedule III.

Prescription drug abuse and misuse are significant public health problems. FDA is serious about confronting these health problems through the coordinated Federal effort outlined in the National Drug Control Strategy. In particular, FDA's CDER shares the concerns of the Substance Abuse and Mental Health Services Administration (SAMHSA) and other Federal agencies about the increased abuse of opioid analgesic medications by adolescents as well as by adults. In HHS databases such as SAMHSA's DAWN, the frequency of emergency room mentions for hydrocodone analgesic combination product misuse/ abuse appears high. However, these very effective, safe Schedule III analgesics are the most commonly prescribed (opioid prescription) analgesics for acute dental, surgical, and perioperative pain as well as for other chronic medical conditions. The combination hydrocodone products are recommended by the WHO Analgesic Ladder and in other pain management guidelines when non-steroidal and over-the-counter medications have proved inadequate to manage pain, and prior to treatment with the higher potency, higher risk, single entity Schedule II opioid analgesics such as morphine, oxycodone, or hydromorphone. When rates of abuse and misuse for hydrocodone-emergency room related mentions are adjusted for the number of retail prescriptions (that is their frequency of use), the rates of abuse and misuse for this class are significantly lower than for oxycodone (Schedule II) analgesics and have remained relatively constant for the last five years. Nevertheless, as previously stated, a recommendation for initial scheduling or rescheduling of a drug requires the evaluation of all the information available at the time of the request.

The determination to impose or not impose stringent controls on a substance or drug is based upon a comprehensive, consistent and uniform evaluation of medical and scientific factors.

Pursuant to Title 21, United States Code (U.S.C.) 811(b) of the CSA, the Secretary of the DHHS is required to consider in a scientific and medical evaluation eight factors determinative of control under the CSA. The eight factors are listed below:

- A. The drug's actual or relative potential for abuse;
- B. Scientific evidence of the drug's pharmacological effects;
- C. Scientific knowledge about the drug or substance in general;
- D. History and current patterns of abuse;
- E. The scope, duration and significance of abuse;
- F. The risk (if any) to the public health;
- G. The drug's psychic or physiologic dependence liability; and
- H. Whether the substance is an immediate precursor of a substance that is already controlled.

Following consideration of the eight factors, the Secretary must make three findings to recommend scheduling of a substance under any of the Schedules of the CSA. To place a substance into Schedule II of the CSA, the substance needs to meet the criteria set forth in 21 U.S.C. 812(b)(2), as follows:

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- A. The drug or other substance has a high potential for abuse;
 - B. 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; and
 - C. Abuse of the drug or other substances may lead to severe psychological or physical dependence.
5. **During the hearing, the Subcommittee discussed several proposals for the creation of a database or databases to monitor the distribution and prescription of controlled substances. What form should such a database take, and who should create and maintain it? Should a single federal database be created? Or should each state create its own database? If the latter, how would we ensure that they would be linked and capable of sharing information with each other?**

Any database to monitor the distribution and prescription of controlled substances would fall under the jurisdiction of DEA. Because DEA is the lead Federal agency in enforcing the CSA, FDA would defer to DEA in determining the most appropriate architecture of such a database.

Thank you for having provided FDA the opportunity of testifying before the Subcommittee. If there are further questions, please let us know.

Sincerely,


for Amit K. Sachdev
Associate Commissioner
for Legislation