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Report to Congressional Requesters

December 2003

PRESCRIPTION DRUGS

OxyContin Abuse and Diversion and Efforts to Address the Problem

GAO-04-110

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GAO Highlights

Highlights of GAO-04-110, a report to congressional requesters

Why GAO Did This Study

Amid heightened awareness that many patients with cancer and other chronic diseases suffer from undertreated pain, the Food and Drug Administration (FDA) approved Purdue Pharma's controlled-release pain reliever OxyContin in 1995. Sales grew rapidly, and by 2001 OxyContin had become the most prescribed brand-name narcotic medication for treating moderate-to-severe pain. In early 2000, reports began to surface about abuse and diversion for illicit use of OxyContin, which contains the opioid oxycodone. GAO was asked to examine concerns about these issues. Specifically, GAO reviewed (1) how OxyContin was marketed and promoted, (2) what factors contributed to the abuse and diversion of OxyContin, and (3) what actions have been taken to address OxyContin abuse and diversion.

What GAO Recommends

To improve efforts to prevent or identify abuse and diversion of controlled substances such as OxyContin, FDA's risk management plan guidance should encourage pharmaceutical manufacturers with new drug applications to submit plans that contain a strategy for identifying potential problems with abuse and diversion. FDA concurred with GAO's recommendation. DEA agreed that such risk management plans are important, and Purdue stated that the report appeared to be fair and balanced.

www.gao.gov/cgi-bin/getrpt?GAO-04-110.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crosse at (202) 512-7119.

What GAO Found

Purdue conducted an extensive campaign to market and promote OxyContin using an expanded sales force to encourage physicians, including primary care specialists, to prescribe OxyContin not only for cancer pain but also as an initial opioid treatment for moderate-to-severe noncancer pain. OxyContin prescriptions, particularly those for noncancer pain, grew rapidly, and by 2003 nearly half of all OxyContin prescribers were primary care physicians. The Drug Enforcement Administration (DEA) has expressed concern that Purdue's aggressive marketing of OxyContin focused on promoting the drug to treat a wide range of conditions to physicians who may not have been adequately trained in pain management. FDA has taken two actions against Purdue for OxyContin advertising violations. Further, Purdue did not submit an OxyContin promotional video for FDA review upon its initial use in 1998, as required by FDA regulations.

Several factors may have contributed to the abuse and diversion of OxyContin. The active ingredient in OxyContin is twice as potent as morphine, which may have made it an attractive target for misuse. Further, the original label's safety warning advising patients not to crush the tablets because of the possible rapid release of a potentially toxic amount of oxycodone may have inadvertently alerted abusers to methods for abuse. Moreover, the significant increase in OxyContin's availability in the marketplace may have increased opportunities to obtain the drug illicitly in some states. Finally, the history of abuse and diversion of prescription drugs, including opioids, in some states may have predisposed certain areas to problems with OxyContin. However, GAO could not assess the relationship between the increased availability of OxyContin and locations of abuse and diversion because the data on abuse and diversion are not reliable, comprehensive, or timely.

Federal and state agencies and Purdue have taken actions to address the abuse and diversion of OxyContin. FDA approved a stronger safety warning on OxyContin's label. In addition, FDA and Purdue collaborated on a risk management plan to help detect and prevent OxyContin abuse and diversion, an approach that was not used at the time OxyContin was approved. FDA plans to provide guidance to the pharmaceutical industry by September 2004 on risk management plans, which are an optional feature of new drug applications. DEA has established a national action plan to prevent abuse and diversion of OxyContin. State agencies have investigated reports of abuse and diversion. In addition to developing a risk management plan, Purdue has initiated several OxyContin-related educational programs, taken disciplinary action against sales representatives who improperly promoted OxyContin, and referred physicians suspected of improper prescribing practices to the authorities.

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Abbreviations

DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Administration
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug and Cosmetic Act
HHS	Department of Health and Human Services
HIDTA	High Intensity Drug Trafficking Area
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
NFLIS	National Forensic Laboratory Information System
ONDCP	Office of National Drug Control Policy
PDUFA	Prescription Drug User Fee Act of 1992
PhRMA	Pharmaceutical Research and Manufacturers of America
RADARS	Researched Abuse, Diversion, and Addiction-Related Surveillance
SAMHSA	Substance Abuse and Mental Health Services Administration
STRIDE	System to Retrieve Information from Drug Evidence
WHO	World Health Organization

GAO
Accountability * Integrity * Reliability

United States General Accounting Office
Washington, DC 20548

December 23, 2003

The Honorable Frank R. Wolf
Chairman
Subcommittee on Commerce, Justice, State, and the Judiciary,
and Related Agencies
Committee on Appropriations
House of Representatives

The Honorable James C. Greenwood
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives

The Honorable Harold Rogers
House of Representatives

Patients with cancer may suffer from fairly constant pain for months or years. Patients with other diseases or conditions, such as rheumatoid arthritis, osteoarthritis, chronic back pain, or sickle cell anemia, may also suffer from pain that lasts for extended periods of time. Since 1986, the World Health Organization (WHO) and others have reported that the inadequate treatment of cancer and noncancer pain is a serious public health concern. To address this concern, efforts have been made to better educate health care professionals on the need to improve the treatment of both cancer and noncancer pain, including the appropriate role of prescription drugs.

Amid the heightened awareness that many people were suffering from undertreated pain, in 1995 the Food and Drug Administration (FDA) approved the new drug OxyContin, a controlled-release semisynthetic opioid analgesic manufactured by Purdue Pharma L.P.,[1] for the treatment of moderate-to-severe pain lasting more than a few days.[2] According to

[1]OxyContin is an opioid analgesic—a narcotic substance that relieves a person's pain without causing the loss of consciousness. Hereafter, we refer to the company as Purdue.

[2]As discussed later in this report, FDA approved the revised OxyContin label in July 2001 to describe the time frame as "when a continuous around-the-clock analgesic is needed for an extended period of time."

Purdue, OxyContin provides patients with continuous relief from pain over a 12-hour period, reduces pain fluctuations, requires fewer daily doses to help patients adhere to their prescribed regimen more easily, allows them to sleep through the night, and allows a physician to increase the OxyContin dose for a patient as needed to relieve pain.[3] Sales of the drug increased rapidly following its introduction to the marketplace in 1996. By 2001, sales had exceeded $1 billion annually, and OxyContin had become the most frequently prescribed brand-name narcotic medication for treating moderate-to-severe pain in the United States.

In early 2000, media reports began to surface in several states that OxyContin was being abused—that is, used for nontherapeutic purposes or for purposes other than those for which it was prescribed—and illegally diverted.[4] According to FDA and the Drug Enforcement Administration (DEA), the abuse of OxyContin is associated with serious consequences, including addiction, overdose, and death.[5] When OxyContin was approved, the federal government classified it as a schedule II controlled substance under the Controlled Substances Act because it has a high potential for abuse and may lead to severe psychological or physical dependence.[6] DEA has characterized the pharmacological effects of OxyContin, and its active ingredient oxycodone, as similar to those of heroin. Media reports indicated that abusers were crushing OxyContin tablets and snorting the powder or dissolving it in water and injecting it to defeat the intended controlled-release effect of the drug and attain a "rush" or "high" through

[3]According to FDA, there is no known limit to the amount of oxycodone, the active ingredient in OxyContin, that can be used to treat pain.

[4]Prescription drug diversion can involve such activities as "doctor shopping" by individuals who visit numerous physicians to obtain multiple prescriptions, prescription forgery, and pharmacy theft. Diversion can also involve illegal sales of prescription drugs by physicians, patients, or pharmacists, as well as obtaining controlled substances from Internet pharmacies without a valid prescription.

[5]According to the National Institute on Drug Abuse, addiction is a chronic, relapsing disease, characterized by compulsive drug seeking and use and by neurochemical and molecular changes in the brain, whereas physical dependence is an adaptive physiological state that can occur with regular drug use and results in withdrawal symptoms when drug use is discontinued.

[6]Under the Controlled Substances Act, which was enacted in 1970, drugs are classified as controlled substances and placed into one of five schedules based on their medicinal value, potential for abuse, and safety or dependence liability. Schedule I drugs have no medicinal value; have not been approved by FDA; and along with schedule II drugs, have the highest potential for abuse. Schedule II drugs have the highest potential for abuse of any approved drugs.

the body's rapid absorption of oxycodone. During a December 2001 congressional hearing, witnesses from DEA and other law enforcement officials from Kentucky, Virginia, and West Virginia described the growing problem of abuse and diversion of OxyContin.[7] Questions were raised about what factors may have caused the abuse and diversion, including whether Purdue's efforts to market the drug may have contributed to the problem. In February 2002, another congressional hearing was conducted on federal, state, and local efforts to decrease the abuse and diversion of OxyContin.[8]

Because of your concerns about these issues, you asked us to examine the marketing and promotion of OxyContin and its abuse and diversion. Specifically, we addressed the following questions:

1. How has Purdue marketed and promoted OxyContin?

2. What factors contributed to the abuse and diversion of OxyContin?

3. What actions have been taken to address OxyContin abuse and diversion?

To identify how Purdue marketed and promoted OxyContin, we interviewed Purdue officials and analyzed company documents and data. We also interviewed selected Purdue sales representatives who were high and midrange sales performers during 2001 and physicians who were among the highest prescribers of OxyContin. To determine how Purdue's marketing and promotion of OxyContin compared to that of other drugs, we examined the promotional materials and information related to FDA actions and interviewed officials from companies that manufacture and market three other opioid drugs, Avinza, Kadian, and Oramorph SR, that like OxyContin are classified as schedule II controlled substances.[9] Because of their concern about the proprietary nature of the information,

[7]*OxyContin*, Hearings of the Subcommittee on the Departments of Commerce, Justice, and State, the Judiciary, and Related Agencies, House Committee on Appropriations, 107th Cong. Part 10 (Dec. 11, 2001).

[8]*OxyContin: Balancing Risks and Benefits*, Hearing of the Senate Committee on Health, Education, Labor, and Pensions, 107th Cong. 287 (Feb. 12, 2002).

[9]Avinza was approved by FDA in 2002 and is marketed by Ligand Pharmaceuticals; Kadian was approved in 1996 and is marketed by Alpharma-US Human Pharmaceuticals; and Oramorph SR was approved in 1991 and is now owned by Élan Corporation, which told us it is not currently marketing the drug.

the three companies that market these drugs did not provide us with the same level of detail about the marketing and promotion of their drugs as did Purdue. We also examined data from DEA on promotional expenditures for OxyContin and two other schedule II controlled substances. To examine what factors may have contributed to the abuse and diversion of OxyContin, we interviewed officials from DEA, FDA, and Purdue and physicians who prescribe OxyContin. We also analyzed IMS Health data on sales of OxyContin nationwide and Purdue's distribution of sales representatives, as part of an effort to compare the areas with large sales growth and more sales representatives per capita with the areas where abuse and diversion problems were identified. However, limitations on the abuse and diversion data prevented an assessment of the relationship between the availability of OxyContin and areas where the drug was abused or diverted. To determine what actions have been taken to address OxyContin abuse and diversion, we interviewed FDA officials and examined FDA information regarding the drug's approval and marketing and promotion. We also interviewed DEA officials and examined how DEA determined the prevalence of OxyContin abuse and diversion nationally. In addition, we examined state efforts to identify those involved in the abuse and diversion of OxyContin. We also reviewed actions taken by Purdue to address this problem. (See app. I for a detailed discussion of our methodology.)

We performed our work from August 2002 through October 2003, in accordance with generally accepted government auditing standards.

Results in Brief

Purdue conducted an extensive campaign to market and promote OxyContin using an expanded sales force and multiple promotional approaches to encourage physicians, including primary care specialists, to prescribe OxyContin as an initial opioid treatment for noncancer pain. OxyContin sales and prescriptions grew rapidly following its market introduction in 1996, with the growth in prescriptions for noncancer pain outpacing the growth in prescriptions for cancer pain from 1997 through 2002. By 2003, nearly half of all OxyContin prescribers were primary care physicians. DEA has expressed concern that Purdue's aggressive marketing of OxyContin focused on promoting the drug to treat a wide range of conditions to physicians who may not have been adequately trained in pain management. Purdue has been cited twice by FDA for using potentially false or misleading medical journal advertisements for OxyContin that violated the Federal Food, Drug and Cosmetic Act (FD&C Act), including one advertisement that failed to include warnings about the potentially fatal risks associated with OxyContin use. Further, Purdue did

not submit an OxyContin promotional video for FDA review at the time of its initial distribution in 1998, as required by FDA regulations. Therefore, FDA did not have the opportunity to review the video at the time of its distribution to ensure that the information it contained was truthful, balanced, and accurately communicated. FDA reviewed a similar video in 2002 and told us that the video appeared to have made unsubstantiated claims about OxyContin and minimized its risks.

Several factors may have contributed to OxyContin's abuse and diversion. OxyContin's controlled-release formulation, which made the drug beneficial for the relief of moderate-to-severe pain over an extended period of time, enabled the drug to contain more of the active ingredient oxycodone than other, non-controlled-release oxycodone-containing drugs. This feature may have made OxyContin an attractive target for abuse and diversion, according to DEA. OxyContin's controlled-release formulation, which delayed the drug's absorption, also led FDA to include language in the original label stating that OxyContin had a lower potential for abuse than other oxycodone products. FDA officials thought that the controlled-release feature would make the drug less attractive to abusers. However, FDA did not recognize that the drug could be dissolved in water and injected, which disrupted the controlled-release characteristics and created an immediate rush or high, thereby increasing the potential for abuse. In addition, the safety warning on the label that advised patients not to crush the tablets because a rapid release of a potentially toxic amount of the drug could result—a customary precaution for controlled-release medications—may have inadvertently alerted abusers to a possible method for misusing the drug. The rapid growth in OxyContin sales, which increased the drug's availability in the marketplace, may have made it easier for abusers to obtain the drug for illicit purposes. Further, some geographic areas have been shown to have a history of prescription drug abuse and diversion that may have predisposed some states to the abuse and diversion of OxyContin. However, we could not assess the relationship between the increased availability of OxyContin and locations where it is being abused and diverted because the data on abuse and diversion are not reliable, comprehensive, or timely.

Since 2000, federal and state agencies and Purdue have taken several actions to try to address abuse and diversion of OxyContin. In July 2001, FDA approved a revised OxyContin label adding the highest level of safety warning that FDA can place on an approved drug product. The agency also collaborated with Purdue to develop and implement a risk management plan to help detect and prevent abuse and diversion of OxyContin. Risk management plans were not used at the time OxyContin was approved.

The plans are an optional feature of new drug applications that are intended to decrease product risks by using one or more interventions or tools beyond the approved product labeling. FDA plans to provide guidance on risk management plans to the pharmaceutical industry by September 2004. Also at the federal level, DEA initiated 257 OxyContin-related abuse and diversion cases in fiscal years 2001 and 2002, which resulted in 302 arrests and about $1 million in fines. At the state level, Medicaid fraud control units have investigated OxyContin abuse and diversion; however, they do not maintain precise data on the number of investigations and enforcement actions completed. Similarly, state medical licensure boards have investigated complaints about physicians who were suspected of abuse and diversion of controlled substances, but they could not provide data on the number of investigations involving OxyContin. Purdue has initiated education programs and other activities for physicians, pharmacists, and the public to address OxyContin abuse and diversion. Purdue has also taken disciplinary action against its sales representatives who improperly promoted OxyContin and has referred physicians who were suspected of misprescribing OxyContin to the appropriate authorities. Although Purdue has used very specific information on physician prescribing practices to market and promote OxyContin since its approval, it was not until October 2002 that Purdue began to use this information and other indicators to identify patterns of prescribing that could point to possible improper sales representative promotion or physician abuse and diversion of OxyContin.

To improve efforts to prevent or identify the abuse and diversion of schedule II controlled substances such as oxycodone, we recommend that FDA's risk management plan guidance encourage the pharmaceutical manufacturers that submit new drug applications for these substances to include plans that contain a strategy for monitoring the use of these drugs and identifying potential abuse and diversion problems.

We received comments on a draft of this report from FDA, DEA, and Purdue. FDA agreed with our recommendation that risk management plans for schedule II controlled substances contain a strategy for monitoring and identifying potential abuse and diversion problems. DEA reiterated its statement that Purdue's aggressive marketing of OxyContin exacerbated the abuse and diversion problems and noted that it is essential that risk management plans be put in place prior to the introduction of controlled substances into the marketplace. Purdue said the report appeared to be fair and balanced, but that we should add the media as one of the factors contributing to abuse and diversion problems

with OxyContin. We incorporated their technical comments where appropriate.

Background

Ensuring that pharmaceuticals are available for those with legitimate medical need while combating the abuse and diversion of prescription drugs involves the efforts of both federal and state government agencies. Under the FD&C Act, FDA is responsible for ensuring that drugs are safe and effective before they are available in the marketplace. The Controlled Substances Act,[10] which is administered by DEA, provides the legal framework for the federal government's oversight of the manufacture and wholesale distribution of controlled substances, that is, drugs and other chemicals that have a potential for abuse. The states address certain issues involving controlled substances through their own controlled substances acts and their regulation of the practice of medicine and pharmacy. In response to concerns about the influence of pharmaceutical marketing and promotional activities on physician prescribing practices, both the pharmaceutical industry and the Department of Health and Human Services's (HHS) Office of Inspector General have issued voluntary guidelines on appropriate marketing and promotion of prescription drugs.

Medical Treatment of Pain

As the incidence and prevalence of painful diseases have grown along with the aging of the population, there has been a growing acknowledgment of the importance of providing effective pain relief. Pain can be characterized in terms of intensity—mild to severe—and duration—acute (sudden onset) or chronic (long term). The appropriate medical treatment varies according to these two dimensions.

In 1986, WHO determined that cancer pain could be relieved in most if not all patients, and it encouraged physicians to prescribe opioid analgesics. WHO developed a three-step analgesic ladder as a practice guideline to provide a sequential use of different drugs for cancer pain management. For the first pain step, treatment with nonopioid analgesics, such as aspirin or ibuprofen, is recommended. If pain is not relieved, then an opioid such as codeine should be used for mild-to-moderate pain as the second step. For the third step—moderate-to-severe pain—opioids such as morphine should be used.

[10]Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (Pub. L. No. 91-513, §§100 et seq., 84 Stat. 1236, 1242 et seq.).

Beginning in the mid-1990s, various national pain-related organizations issued pain treatment and management guidelines, which included the use of opioid analgesics in treating both cancer and noncancer pain. In 1995, the American Pain Society recommended that pain should be treated as the fifth vital sign[11] to ensure that it would become common practice for health care providers to ask about pain when conducting patient evaluations. The practice guidelines issued by the Agency for Health Care Policy and Research provided physicians and other health care professionals with information on the management of acute pain in 1992 and cancer pain in 1994, respectively.[12] Health care providers and hospitals were further required to ensure that their patients received appropriate pain treatment when the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), a national health care facility standards-setting and accrediting body, implemented its pain standards for hospital accreditation in 2001.

OxyContin

OxyContin, a schedule II drug manufactured by Purdue Pharma L.P., was approved by FDA in 1995 for the treatment of moderate-to-severe pain lasting more than a few days, as indicated in the original label.[13] OxyContin followed Purdue's older product, MS Contin, a morphine-based product that was approved in 1984 for a similar intensity and duration of pain and during its early years of marketing was promoted for the treatment of cancer pain. The active ingredient in OxyContin tablets is oxycodone, a compound that is similar to morphine and is also found in oxycodone-combination pain relief drugs such as Percocet, Percodan, and Tylox. Because of its controlled-release property, OxyContin contains more active ingredient and needs to be taken less often (twice a day) than these

[11]The other four vital signs physicians use to assess patients are pulse, blood pressure, core temperature, and respiration.

[12]In 1999, the name of the Agency for Health Care Policy and Research was changed to the Agency for Healthcare Research and Quality. The agency, which is part of HHS, is responsible for supporting research designed to improve the quality of health care, reduce its costs, and broaden access to essential services.

[13]When we refer to OxyContin's label we are also referring to the drug's package insert that contains the same information about the product.

other oxycodone-containing drugs.[14] The OxyContin label originally approved by FDA indicated that the controlled-release characteristics of OxyContin were believed to reduce its potential for abuse. The label also contained a warning that OxyContin tablets were to be swallowed whole, and were not to be broken, chewed, or crushed because this could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. Such a safety warning is customary for schedule II controlled-release medications. FDA first approved the marketing and use of OxyContin in 10-, 20-, and 40-milligram controlled-release tablets. FDA later approved 80- and 160-milligram controlled-release tablets for use by patients who were already taking opioids.[15] In July 2001, FDA approved the revised label to state that the drug is approved for the treatment of moderate-to-severe pain in patients who require "a continuous around-the-clock analgesic for an extended period of time." (See app. II for a summary of the changes that were made by FDA to the original OxyContin label.)

OxyContin sales and prescriptions grew rapidly following its market introduction in 1996. Fortuitous timing may have contributed to this growth, as the launching of the drug occurred during the national focus on the inadequacy of patient pain treatment and management. In 1997, OxyContin's sales and prescriptions began increasing significantly, and they continued to increase through 2002. In both 2001 and 2002, OxyContin's sales exceeded $1 billion, and prescriptions were over 7 million. The drug became Purdue's main product, accounting for 90 percent of the company's total prescription sales by 2001.

Media reports of OxyContin abuse and diversion began to surface in 2000. These reports first appeared in rural areas of some states, generally in the Appalachian region, and continued to spread to other rural areas and larger cities in several states. Rural communities in Maine, Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia were reportedly being devastated by the abuse and diversion of OxyContin. For example, media reports told of persons and communities that had been adversely affected by the rise of addiction and deaths related to OxyContin. One report noted that drug

[14]For example, according to Purdue's comparable dose guide a patient taking one Percodan 4.5-milligram tablet or one Tylox 5-milligram tablet every 6 hours can be converted to either a 10- or a 20-milligram OxyContin tablet to be taken every 12 hours. For a 12-hour dosing period, one OxyContin tablet replaces two Percodan or Tylox tablets, and one OxyContin tablet contains twice as much oxycodone as one of the other tablets.

[15]In April 2001, Purdue discontinued distribution of the 160-milligram tablets because of OxyContin abuse and diversion concerns.

treatment centers and emergency rooms in a particular area were receiving new patients who were addicted to OxyContin as early as 1999. Pain patients, teens, and recreational drug users who had abused OxyContin reportedly entered drug treatment centers sweating and vomiting from withdrawal. In West Virginia, as many as one-half of the approximately 300 patients admitted to a drug treatment clinic in 2000 were treated for OxyContin addiction. The media also reported on deaths due to OxyContin. For example, a newspaper's investigation of autopsy reports involving oxycodone-related deaths found that OxyContin had been involved in over 200 overdose deaths in Florida since 2000.[16] In another case, a forensic toxicologist commented that he had reviewed a number of fatal overdose cases in which individuals took a large dose of OxyContin, in combination with alcohol or other drugs.

After learning about the initial reports of abuse and diversion of OxyContin in Maine in 2000, Purdue formed a response team made up of its top executives and physicians to initiate meetings with federal and state officials in Maine to gain an understanding of the scope of the problem and to devise strategies for preventing abuse and diversion. After these meetings, Purdue distributed brochures to health care professionals that described several steps that could be taken to prevent prescription drug abuse and diversion. In response to the abuse and diversion reports, DEA analyzed data collected from medical examiner autopsy reports and crime scene investigation reports. The most recent data available from DEA show that as of February 2002, the agency had verified 146 deaths nationally involving OxyContin in 2000 and 2001.

According to Purdue, as of early October 2003, over 300 lawsuits concerning OxyContin were pending against Purdue, and 50 additional lawsuits had been dismissed. The cases involve many allegations, including, for example, that Purdue used improper sales tactics and overpromoted OxyContin causing the drug to be inappropriately prescribed by physicians, and that Purdue took inadequate actions to prevent addiction, abuse, and diversion of the drug. The lawsuits have been brought in 25 states and the District of Columbia in both federal and state courts.

[16]Doris Bloodsworth, "Pain Pill Leaves Death Trail: A Nine-Month Investigation Raises Many Questions about Purdue Pharma's Powerful Drug OxyContin," *Orlando Sentinel*, Oct. 19, 2003.

Controlled Substances Act

The Controlled Substances Act established a classification structure for drugs and chemicals used in the manufacture of drugs that are designated as controlled substances.[17] Controlled substances are classified by DEA into five schedules on the basis of their medicinal value, potential for abuse, and safety or dependence liability. Schedule I drugs—including heroin, marijuana, and LSD—have a high potential for abuse and no currently accepted medical use. Schedule II drugs—which include opioids such as morphine and oxycodone, the primary ingredient in OxyContin—have a high potential for abuse among drugs with an accepted medical use and may lead to severe psychological or physical dependence. Drugs on schedules III through V have medical uses and successively lower potentials for abuse and dependence. Schedule III drugs include anabolic steroids, codeine, hydrocodone in combination with aspirin or acetaminophen, and some barbiturates. Schedule IV contains such drugs as the antianxiety drugs diazepam (Valium) and alprazolam (Xanax). Schedule V includes preparations such as cough syrups with codeine. All scheduled drugs except those in schedule I are legally available to the public with a prescription.[18]

FDA's Regulation of Prescription Drugs

Under the FD&C Act and implementing regulations, FDA is responsible for ensuring that all new drugs are safe and effective. FDA reviews scientific and clinical data to decide whether to approve drugs based on their intended use, effectiveness, and the risks and benefits for the intended population, and also monitors drugs for continued safety after they are in use.

FDA also regulates the advertising and promotion of prescription drugs under the FD&C Act. FDA carries out this responsibility by ensuring that prescription drug advertising and promotion is truthful, balanced, and accurately communicated.[19] The FD&C Act makes no distinction between

[17]Section 201, classified to 21 U.S.C. § 811.

[18]Some schedule V drugs that contain limited quantities of certain narcotic and stimulant drugs are available over the counter, without a prescription.

[19]FDA regulations require that promotional labeling and advertisements be submitted to FDA at the time of initial dissemination (for labeling) and initial publication (for advertisements). The FD&C Act defines labeling to include all labels and other written, printed, or graphic matter accompanying an article. For example, promotional materials commonly shown or given to physicians, such as sales aids and branded promotional items, are regulated as promotional labeling. FDA may also regulate promotion by sales representatives on computer programs, through fax machines, or on electronic bulletin boards.

controlled substances and other prescription drugs in the oversight of promotional activities. FDA told us that the agency takes a risk-based approach to enforcement, whereby drugs with more serious risks, such as opioids, are given closer scrutiny in monitoring promotional messages and activities, but the agency has no specific guidance or policy on this approach. The FD&C Act and its implementing regulations require that all promotional materials for prescription drugs be submitted to FDA at the time the materials are first disseminated or used, but it generally is not required that these materials be approved by FDA before their use. As a result, FDA's actions to address violations occur after the materials have already appeared in public. In fiscal year 2002, FDA had 39 staff positions dedicated to oversight of drug advertising and promotion of all pharmaceuticals distributed in the United States. According to FDA, most of the staff focuses on the oversight of promotional communications to physicians. FDA officials told us that in 2001 it received approximately 34,000 pieces of promotional material, including consumer advertisements and promotions to physicians, and received and reviewed 230 complaints about allegedly misleading advertisements, including materials directed at health professionals.[20]

FDA issues two types of letters to address violations of the FD&C Act: untitled letters and warning letters. Untitled letters are issued for violations such as overstating the effectiveness of the drug, suggesting a broader range of indicated uses than the drug has been approved for, and making misleading claims because of inadequate context or lack of balanced information. Warning letters are issued for more serious violations, such as those involving safety or health risks, or for continued violations of the act. Warning letters generally advise a pharmaceutical manufacturer that FDA may take further enforcement actions, such as seeking judicial remediation, without notifying the company and may ask the manufacturer to conduct a new advertising campaign to correct inaccurate impressions left by the advertisements.

Under the Controlled Substances Act, FDA notifies DEA if FDA is reviewing a new drug application for a drug that has a stimulant, depressant, or hallucinogenic effect on the central nervous system and has abuse potential. FDA performs a medical and scientific assessment as

[20]For details on FDA's oversight of drug advertising see U.S. General Accounting Office, *Prescription Drugs: FDA Oversight of Direct-to-Consumer Advertising Has Limitations*, GAO-03-177 (Washington, D.C.: Oct. 28, 2002).

required by the Controlled Substances Act, and recommends to DEA an initial schedule level to be assigned to a new controlled substance.

FDA plans to provide guidance to the pharmaceutical industry on the development, implementation, and evaluation of risk management plans as a result of the reauthorization of the Prescription Drug User Fee Act of 1992 (PDUFA).[21] FDA expects to issue this guidance by September 30, 2004. FDA defines a risk management program as a strategic safety program that is designed to decrease product risks by using one or more interventions or tools beyond the approved product labeling. Interventions used in risk management plans may include postmarketing surveillance, education and outreach programs to health professionals or consumers, informed consent agreements for patients, limitations on the supply or refills of products, and restrictions on individuals who may prescribe and dispense drug products. All drug manufacturers have the option to develop and submit risk management plans to FDA as part of their new drug applications.

DEA's Regulation of Controlled Substances

DEA is the primary federal agency responsible for enforcing the Controlled Substances Act. DEA has the authority to regulate transactions involving the sale and distribution of controlled substances at the manufacturer and wholesale distributor levels. DEA registers legitimate handlers of controlled substances—including manufacturers, distributors, hospitals, pharmacies, practitioners, and researchers—who must comply with regulations relating to drug security and accountability through the maintenance of inventories and records. All registrants, including pharmacies, are required to maintain records of controlled substances that have been manufactured, purchased, and sold. Manufacturers and distributors are also required to report their annual inventories of controlled substances to DEA. The data provided to DEA are available for use in monitoring the distribution of controlled substances throughout the United States and identifying retail-level registrants that received unusual quantities of controlled substances. DEA regulations for schedule II prescription drugs, unlike those for other prescription drugs, require that each prescription must be written and signed by the physician and may not be telephoned in to the pharmacy except in an emergency. Also, a

[21]The Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, title I, 106 Stat. 4491, was reauthorized by the Food and Drug Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296, and, most recently, by the Prescription Drug User Fee Amendments of 2002, Pub. L. No. 107-188, title V, subtitle A, 116 Stat. 594, 687.

prescription for a schedule II drug may not be refilled. A physician is required to provide a new prescription each time a patient obtains more of the drug. DEA also sets limits on the quantity of schedule II controlled substances that may be produced in the United States in any given year. Specifically, DEA sets aggregate production quotas that limit the production of bulk raw materials used in the manufacture of controlled substances. DEA determines these quotas based on a variety of data including sales, production, inventories, and exports. Individual companies must apply to DEA for manufacturing or procurement quotas for specific pharmaceutical products. For example, Purdue has a procurement quota for oxycodone, the principle ingredient in OxyContin, that allows the company to purchase specified quantities of oxycodone from bulk manufacturers.

States' Regulation of the Practice of Medicine and Pharmacy and Role in Monitoring Illegal Use and Diversion of Prescription Drugs

State laws govern the prescribing and dispensing of prescription drugs by licensed health care professionals. Each state requires that physicians practicing in the state be licensed, and state medical practice laws generally outline standards for the practice of medicine and delegate the responsibility of regulating physicians to state medical boards. States also require pharmacists and pharmacies to be licensed. The regulation of the practice of pharmacy is based on state pharmacy practice acts and regulations enforced by the state boards of pharmacy. According to the National Association of Boards of Pharmacy, all state pharmacy laws require that records of prescription drugs dispensed to patients be maintained and that state pharmacy boards have access to the prescription records. State regulatory boards face new challenges with the advent of Internet pharmacies, because they enable pharmacies and physicians to anonymously reach across state borders to prescribe, sell, and dispense prescription drugs without complying with state requirements.[22] In some cases, consumers can purchase prescription drugs, including controlled substances, such as OxyContin, from Internet pharmacies without a valid prescription.

[22]For more details on Internet pharmacies, see U.S. General Accounting Office, *Internet Pharmacies: Adding Disclosure Requirements Would Aid State and Federal Oversight*, GAO-01-69 (Washington, D.C.: Oct. 19, 2000).

In addition to these regulatory boards, 15 states operate prescription drug monitoring programs as a means to control the illegal diversion of prescription drugs that are controlled substances. Prescription drug monitoring programs are designed to facilitate the collection, analysis, and reporting of information on the prescribing, dispensing, and use of controlled substances within a state. They provide data and analysis to state law enforcement and regulatory agencies to assist in identifying and investigating activities potentially related to the illegal prescribing, dispensing, and procuring of controlled substances. For example, physicians in Kentucky can use the program to check a patient's prescription drug history to determine if the individual may be "doctor shopping" to seek multiple controlled substance prescriptions. An overriding goal of prescription drug monitoring programs is to support both the state laws ensuring access to appropriate pharmaceutical care by citizens and the state laws deterring diversion. As we have reported, state prescription drug monitoring programs offer state regulators an efficient means of detecting and deterring illegal diversion. However, few states proactively analyze prescription data to identify individuals, physicians, or pharmacies that have unusual use, prescribing, or dispensing patterns that may suggest potential drug diversion or abuse. Although three states can respond to requests for information within 3 to 4 hours, providing information on suspected illegal prescribing, dispensing, or doctor shopping at the time a prescription is written or sold would require states to improve computer capabilities. In addition, state prescription drug monitoring programs may require additional legal authority to analyze data proactively.[23]

Guidelines for Marketing Drugs to Health Care Professionals

At the time that OxyContin was first marketed, there were no industry or federal guidelines for the promotion of prescription drugs. Voluntary guidelines regarding how drug companies should market and promote their drugs to health care professionals were issued in July 2002 by the Pharmaceutical Research and Manufacturers of America (PhRMA). In April 2003, HHS's Office of Inspector General issued voluntary guidelines for how drug companies should market and promote their products to federal health care programs. Neither set of guidelines distinguishes between controlled and noncontrolled substances.

[23]For more details on these programs, see U.S. General Accounting Office, *Prescription Drugs: State Monitoring Programs Provide Useful Tool to Reduce Diversion*, GAO-02-634 (Washington, D.C.: May 17, 2002).

PhRMA's voluntary code of conduct for sales representatives states that interactions with health care professionals should be to inform these professionals about products, to provide scientific and educational information, and to support medical research and education.[24] The question-and-answer section of the code addresses companies' use of branded promotional items, stating, for example, that golf balls and sports bags should not be distributed because they are not primarily for the benefit of patients, but that speaker training programs held at golf resorts may be acceptable if participants are receiving extensive training. Purdue adopted the code.

In April 2003, HHS's Office of Inspector General issued final voluntary guidance for drug companies' interactions with health care professionals in connection with federal health care programs, including Medicare and Medicaid. Among the guidelines were cautions for companies against offering inappropriate travel, meals, and gifts to influence the prescribing of drugs; making excessive payments to physicians for consulting and research services; and paying physicians to switch their patients from competitors' drugs.

Purdue Conducted an Extensive Campaign to Market and Promote OxyContin

Purdue conducted an extensive campaign to market and promote OxyContin that focused on encouraging physicians, including those in primary care specialties, to prescribe the drug for noncancer as well as cancer pain. To implement its OxyContin campaign, Purdue significantly increased its sales force and used multiple promotional approaches. OxyContin sales and prescriptions grew rapidly following its market introduction, with the growth in prescriptions for noncancer pain outpacing the growth in prescriptions for cancer pain. DEA has expressed concern that Purdue marketed OxyContin for a wide variety of conditions to physicians who may not have been adequately trained in pain management. Purdue has been cited twice by FDA for OxyContin advertisements in medical journals that violated the FD&C Act. FDA has also taken similar actions against manufacturers of two of the three comparable schedule II controlled substances we examined, to ensure that

[24]In addition, the American Medical Association, a professional association for physicians, issued guidelines in 1990 regarding gifts given to physicians by drug industry representatives. For example, physicians may accept individual gifts of nominal value that are related to their work, such as notepads and pens, and may attend conferences sponsored by drug companies that are educational and for which appropriate disclosure of financial support or conflicts of interest is made.

their marketing and promotion were truthful, balanced, and accurately communicated. In addition, Purdue provided two promotional videos to physicians that, according to FDA appear to have made unsubstantiated claims and minimized the risks of OxyContin. The first video was available for about 3 years without being submitted to FDA for review.

Purdue Focused on Promoting OxyContin for Treatment of Noncancer Pain

From the outset of the OxyContin marketing campaign, Purdue promoted the drug to physicians for noncancer pain conditions that can be caused by arthritis, injuries, and chronic diseases, in addition to cancer pain. Purdue directed its sales representatives to focus on the physicians in their sales territories who were high opioid prescribers. This group included cancer and pain specialists, primary care physicians, and physicians who were high prescribers of Purdue's older product, MS Contin. One of Purdue's goals was to identify primary care physicians who would expand the company's OxyContin prescribing base. Sales representatives were also directed to call on oncology nurses, consultant pharmacists, hospices, hospitals, and nursing homes.

From OxyContin's launch until its July 2001 label change, Purdue used two key promotional messages for primary care physicians and other high prescribers. The first was that physicians should prescribe OxyContin for their pain patients both as the drug "to start with and to stay with." The second contrasted dosing with other opioid pain relievers with OxyContin dosing as "the hard way versus the easy way" to dose because OxyContin's twice-a-day dosing was more convenient for patients.[25] Purdue's sales representatives promoted OxyContin to physicians as an initial opioid treatment for moderate-to-severe pain lasting more than a few days, to be prescribed instead of other single-entity opioid analgesics or short-acting combination opioid pain relievers. Purdue has stated that by 2003 primary care physicians had grown to constitute nearly half of all OxyContin prescribers, based on data from IMS Health, an information service providing pharmaceutical market research. DEA's analysis of physicians prescribing OxyContin found that the scope of medical specialties was wider for OxyContin than five other controlled-release, schedule II narcotic analgesics. DEA expressed concern that this resulted in

[25]Following OxyContin's July 2001 label change, Purdue modified its promotional messages but continued to focus on encouraging physicians to prescribe OxyContin for patients taking pain relievers every 4 to 6 hours. In 2003, Purdue began using the promotional claim "there can be life with relief" in OxyContin promotion.

OxyContin's being promoted to physicians who were not adequately trained in pain management.

Purdue's promotion of OxyContin for the treatment of noncancer pain contributed to a greater increase in prescriptions for noncancer pain than for cancer pain from 1997 through 2002.[26] According to IMS Health data, the annual number of OxyContin prescriptions for noncancer pain increased nearly tenfold, from about 670,000 in 1997 to about 6.2 million in 2002.[27] In contrast, during the same 6 years, the annual number of OxyContin prescriptions for cancer pain increased about fourfold, from about 250,000 in 1997 to just over 1 million in 2002. The noncancer prescriptions therefore increased from about 73 percent of total OxyContin prescriptions to about 85 percent during that period, while the cancer prescriptions decreased from about 27 percent of the total to about 15 percent. IMS Health data indicated that prescriptions for other schedule II opioid drugs, such as Duragesic[28] and morphine products, for noncancer pain also increased during this period. Duragesic prescriptions for noncancer pain were about 46 percent of its total prescriptions in 1997, and increased to about 72 percent of its total in 2002. Morphine products, including, for example, Purdue's MS Contin, also experienced an increase in their noncancer prescriptions during the same period. Their noncancer prescriptions were about 42 percent of total prescriptions in 1997, and increased to about 65 percent in 2002. DEA has cited Purdue's focus on promoting OxyContin for treating a wide range of conditions as one of the reasons the agency considered Purdue's marketing of OxyContin to be overly aggressive.

[26]IMS Health reported noncancer prescriptions written for the following types of pain conditions: surgical aftercare; musculoskeletal disorders including back and neck disorders, arthritis conditions, and injuries and trauma including bone fractures; central nervous system disorders including headache conditions such as migraines; genitourinary disorders including kidney stones; and other types of general pain.

[27]The IMS Health data included information from the National Disease and Therapeutics Index and the National Prescription Audit. The National Disease and Therapeutics Index does not capture data from anesthesiologists and dental specialties. The National Prescription Audit data include retail pharmacy, long-term-care, and mail-order prescriptions.

[28]Duragesic is a skin patch used to deliver the opioid pain reliever fentanyl over a 72-hour period.

Purdue Significantly Increased Its Sales Force to Market and Promote OxyContin

Purdue significantly increased its sales force to market and promote OxyContin to physicians and other health care practitioners. In 1996, Purdue began promoting OxyContin with a sales force of approximately 300 representatives in its Prescription Sales Division.[29] Through a 1996 copromotion agreement, Abbott Laboratories provided at least another 300 representatives, doubling the total OxyContin sales force.[30] By 2000, Purdue had more than doubled its own internal sales force to 671. The expanded sales force included sales representatives from the Hospital Specialty Division, which was created in 2000 to increase promotional visits on physicians located in hospitals. (See table 1.)

Table 1: Sales Representative Positions Available for OxyContin Promotion, 1996 through 2002

Positions available[a]	1996	1997	1998	1999	2000	2001	2002
Purdue Prescription Sales Division	318	319	377	471	562	641	641
Purdue Hospital Specialty Division	0	0	0	0	109	125	126
Subtotal—All Purdue sales representatives	**318**	**319**	**377**	**471**	**671**	**766**	**767**
Abbott Laboratories sales representatives[b]	300	300	300	300	300	300	300
Total	**618**	**619**	**677**	**771**	**971**	**1,066**	**1,067**

Source: GAO analysis of Purdue data.

[a]All positions were not necessarily filled in a given year.

[b]Under the OxyContin copromotion agreement, Abbott Laboratories provided at least 300 sales representatives each year.

The manufacturers of two of the three comparable schedule II drugs have smaller sales forces than Purdue. Currently, the manufacturer of Kadian has about 100 sales representatives and is considering entering into a copromotion agreement. Elan, the current owner of Oramorph SR, has approximately 300 representatives, but told us that it is not currently marketing Oramorph SR. The manufacturer of Avinza had approximately 50 representatives at its product launch. In early 2003, Avinza's manufacturer announced that more than 700 additional sales

[29]These sales representatives were also responsible for promoting other Purdue products.

[30]Abbott Laboratories sales representatives' promotion of OxyContin is limited to hospital-based anesthesiologists and surgeons and major hospitals, medical centers, and freestanding pain clinics.

representatives would be promoting the drug under its copromotion agreement with the pharmaceutical manufacturer Organon—for a total of more than 800 representatives.

By more than doubling its total sales representatives, Purdue significantly increased the number of physicians to whom it was promoting OxyContin. Each Purdue sales representative has a specific sales territory and is responsible for developing a list of about 105 to 140 physicians to call on who already prescribe opioids or who are candidates for prescribing opioids. In 1996, the 300-plus Purdue sales representatives had a total physician call list of approximately 33,400 to 44,500. By 2000, the nearly 700 representatives had a total call list of approximately 70,500 to 94,000 physicians. Each Purdue sales representative is expected to make about 35 physician calls per week and typically calls on each physician every 3 to 4 weeks. Each hospital sales representative is expected to make about 50 calls per week and typically calls on each facility every 4 weeks.

Purdue stated it offered a "better than industry average" salary and sales bonuses to attract top sales representatives and provide incentives to boost OxyContin sales as it had done for MS Contin. Although the sales representatives were primarily focused on OxyContin promotion, the amount of the bonus depended on whether a representative met the sales quotas in his or her sales territory for all company products. As OxyContin's sales increased, Purdue's growth-based portion of the bonus formula increased the OxyContin sales quotas necessary to earn the same base sales bonus amounts. The amount of total bonuses that Purdue estimated were tied to OxyContin sales increased significantly from about $1 million in 1996, when OxyContin was first marketed, to about $40 million in 2001. Beginning in 2000, when the newly created hospital specialty representatives began promoting OxyContin, their estimated total bonuses were approximately $6 million annually. In 2001, the average annual salary for a Purdue sales representative was $55,000, and the average annual bonus was $71,500. During the same year, the highest annual sales bonus was nearly $240,000, and the lowest was nearly $15,000. In 2001, Purdue decided to limit the sales bonus a representative could earn based on the growth in prescribing of a single physician after a meeting with the U.S. Attorney for the Western District of Virginia at which the company was informed of the possibility that a bonus could be based on the prescribing of one physician.

Purdue Employed Multiple Approaches to Market and Promote OxyContin

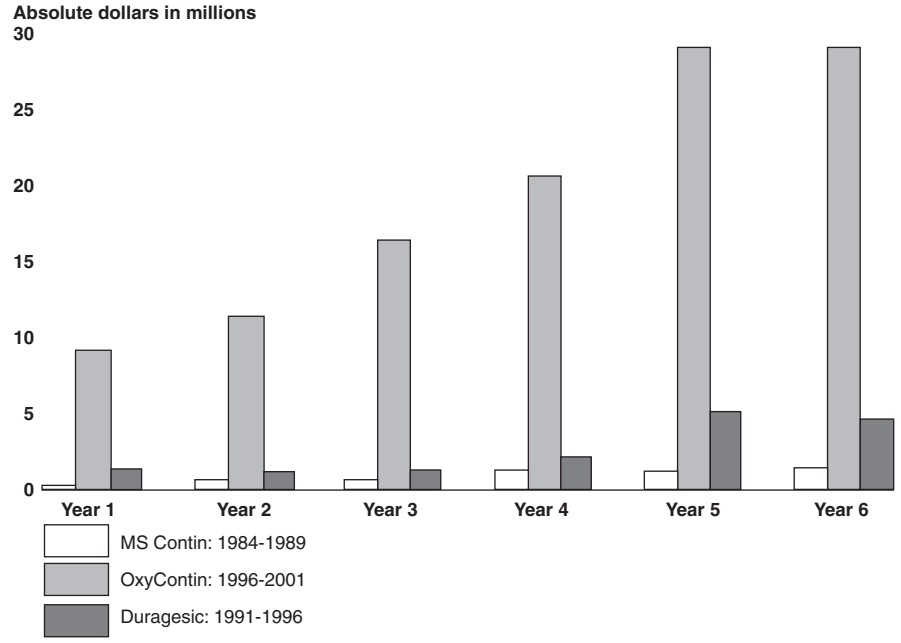
In addition to expanding its sales force, Purdue used multiple approaches to market and promote OxyContin. These approaches included expanding its physician speaker bureau and conducting speaker training conferences, sponsoring pain-related educational programs, issuing OxyContin starter coupons for patients' initial prescriptions, sponsoring pain-related Web sites, advertising OxyContin in medical journals, and distributing OxyContin marketing items to health care professionals.

In our report on direct-to-consumer advertising, we found that most promotional spending is targeted to physicians.[31] For example, in 2001, 29 percent of spending on pharmaceutical promotional activities was related to activities of pharmaceutical sales representatives directed to physicians, and 2 percent was for journal advertising—both activities Purdue uses for its OxyContin promotion. The remaining 69 percent of pharmaceutical promotional spending involved sampling (55 percent), which is the practice of providing drug samples during sales visits to physician offices, and direct-to-consumer advertising (14 percent)—both activities that Purdue has stated it does not use for OxyContin.

According to DEA's analysis of IMS Health data, Purdue spent approximately 6 to 12 times more on promotional efforts during OxyContin's first 6 years on the market than it had spent on its older product, MS Contin, during its first 6 years, or than had been spent by Janssen Pharmaceutical Products, L.P., for one of OxyContin's drug competitors, Duragesic. (See fig. 1.)

[31]U.S. General Accounting Office, *Prescription Drugs: FDA Oversight of Direct-to-Consumer Advertising Has Limitations*, GAO-03-177 (Washington, D.C.: Oct. 28, 2002).

Figure 1: Promotional Spending for Three Opioid Analgesics in First 6 Years of Sales



Source: DEA and IMS Health, Integrated Promotional Service Audit.

Note: Dollars are 2002 adjusted.

During the first 5 years that OxyContin was marketed, Purdue conducted over 40 national pain management and speaker training conferences, usually in resort locations such as Boca Raton, Florida, and Scottsdale, Arizona, to recruit and train health care practitioners for its national speaker bureau. The trained speakers were then made available to speak about the appropriate use of opioids, including oxycodone, the active ingredient in OxyContin, to their colleagues in various settings, such as local medical conferences and grand round presentations in hospitals involving physicians, residents, and interns. Over the 5 years, these conferences were attended by more than 5,000 physicians, pharmacists, and nurses, whose travel, lodging, and meal costs were paid by the company. Purdue told us that less than 1 percent annually of the physicians called on by Purdue sales representatives attended these conferences. Purdue told us it discontinued conducting these conferences in fall 2000. Purdue's speaker bureau list from 1996 through mid-2002 included nearly 2,500 physicians, of whom over 1,000 were active participants. Purdue has paid participants a fee for speaking based on the physician's qualifications; the type of program and time commitment

involved; and expenses such as airfare, hotel, and food. The company currently marketing the comparable drug Avinza has a physician speaker bureau, but does not sponsor speaker training and conferences at resort locations. Kadian's current company does not have a physician speaker bureau and has not held any conferences.

From 1996, when OxyContin was introduced to the market, to July 2002, Purdue has funded over 20,000 pain-related educational programs through direct sponsorship or financial grants. These grants included support for programs to provide physicians with opportunities to earn required continuing medical education credits, such as grand round presentations at hospitals and medical education seminars at state and local medical conferences. During 2001 and 2002, Purdue funded a series of nine programs throughout the country to educate hospital physicians and staff on how to comply with JCAHO's pain standards for hospitals and to discuss postoperative pain treatment. Purdue was one of only two drug companies that provided funding for JCAHO's pain management educational programs.[32] Under an agreement with JCAHO, Purdue was the only drug company allowed to distribute certain educational videos and a book about pain management; these materials were also available for purchase from JCAHO's Web site. Purdue's participation in these activities with JCAHO may have facilitated its access to hospitals to promote OxyContin.

For the first time in marketing any of its products, Purdue used a patient starter coupon program for OxyContin to provide patients with a free limited-time prescription. Unlike patient assistance programs, which provide free prescriptions to patients in financial need, a coupon program is intended to enable a patient to try a new drug through a one-time free prescription. A sales representative distributes coupons to a physician, who decides whether to offer one to a patient, and then the patient redeems it for a free prescription through a participating pharmacy. The program began in 1998 and ran intermittently for 4 years. In 1998 and 1999, each sales representative had 25 coupons that were redeemable for a free 30-day supply. In 2000 each representative had 90 coupons for a 7-day supply, and in 2001 each had 10 coupons for a 7-day supply. Approximately 34,000 coupons had been redeemed nationally when the

[32]During 2000 through 2002, JCAHO sponsored a series of educational programs on pain management standards with various cosponsors, including pain-related groups such as the American Pain Society and the American Academy of Pain Medicine.

program was terminated following the July 2001 OxyContin label change. The manufacturers of two of the comparable drugs we examined—Avinza and Kadian—used coupon programs to introduce patients to their products. Avinza's coupon program requires patients to make a copayment to cover part of the drug's cost.

Purdue has also used Web sites to provide pain-related information to consumers and others. In addition to its corporate Web site, which provides product information, Purdue established the "Partners Against Pain" Web site in 1997 to provide consumers with information about pain management and pain treatment options. According to FDA, the Web site also contained information about OxyContin. Separate sections provide information for patients and caregivers, medical professionals, and institutions. The Web site includes a "Find a Doctor" feature to enable consumers to find physicians who treat pain in their geographic area.[33] As of July 2002, over 33,000 physicians were included. Ligand, which markets Avinza, one of the comparable drugs, has also used a corporate Web site to provide product information. Purdue has also funded Web sites, such as FamilyPractice.com, that provide physicians with free continuing medical educational programs on pain management.[34] Purdue has also provided funding for Web site development and support for health care groups such as the American Chronic Pain Association and the American Academy of Pain Medicine. In addition, Purdue is one of 28 corporate donors—which include all three comparable drug companies—listed on the Web site of the American Pain Society, the mission of which is to improve pain-related education, treatment, and professional practice. Purdue also sponsors painfullyobvious.com, which it describes as a youth-focused "message campaign designed to provide information—and stimulate open discussions—on the dangers of abusing prescription drugs."

Purdue also provided its sales representatives with 14,000 copies of a promotional video in 1999 to distribute to physicians. Entitled *From One Pain Patient to Another: Advice from Patients Who Have Found Relief*, the video was to encourage patients to report their pain and to alleviate patients' concerns about taking opioids. Purdue stated that the video was to be used "in physician waiting rooms, as a 'check out' item for an office's

[33]The "Find a Doctor" feature is a physician listing service provided by the National Physicians DataSource, LLC.

[34]Purdue has also helped to fund the Dannemiller Memorial Education Foundation and the American Academy of Physician Assistants Web sites.

patient education library, or as an educational tool for office or hospital staff to utilize with patients and their families." Copies of the video were also available for ordering on the "Partners Against Pain" Web site from June 2000 through July 2001. The video did not need to be submitted to FDA for its review because it did not contain any information about OxyContin. However, the video included a statement that opioid analgesics have been shown to cause addiction in less than 1 percent of patients. According to FDA, this statement has not been substantiated.

As part of its marketing campaign, Purdue distributed several types of branded promotional items to health care practitioners. Among these items were OxyContin fishing hats, stuffed plush toys, coffee mugs with heat-activated messages, music compact discs, luggage tags, and pens containing a pullout conversion chart showing physicians how to calculate the dosage to convert a patient to OxyContin from other opioid pain relievers.[35] In May 2002, in anticipation of PhRMA's voluntary guidance for sales representatives' interactions with health care professionals, Purdue instructed its sales force to destroy any remaining inventory of non-health-related promotional items, such as stuffed toys or golf balls. In early 2003, Purdue began distributing an OxyContin branded goniometer—a range and motion measurement guide. According to DEA, Purdue's use of branded promotional items to market OxyContin was unprecedented among schedule II opioids, and was an indicator of Purdue's aggressive and inappropriate marketing of OxyContin.

Another approach Purdue used to promote OxyContin was to place advertisements in medical journals. Purdue's annual spending for OxyContin advertisements increased from about $700,000 in 1996 to about $4.6 million in 2001. All three companies that marketed the comparable drugs have also used medical journal advertisements to promote their products.

OxyContin Advertisements Violated the FD&C Act

Purdue has been cited twice by FDA for using advertisements in professional medical journals that violated the FD&C Act. In May 2000, FDA issued an untitled letter to Purdue regarding a professional medical

[35]It is common drug industry practice for companies to provide conversion tables for sales representatives to distribute to health care practitioners. Purdue used a similar pen for its older product, MS Contin.

journal advertisement for OxyContin.[36] FDA noted that among other problems, the advertisement implied that OxyContin had been studied for all types of arthritis pain when it had been studied only in patients with moderate-to-severe osteoarthritis pain, the advertisement suggested OxyContin could be used as an initial therapy for the treatment of osteoarthritis pain without substantial evidence to support this claim, and the advertisement promoted OxyContin in a selected class of patients—the elderly—without presenting risk information applicable to that class of patients.[37] Purdue agreed to stop dissemination of the advertisement. The second action taken by FDA was more serious. In January 2003, FDA issued a warning letter to Purdue regarding two professional medical journal advertisements for OxyContin that minimized its risks and overstated its efficacy, by failing to prominently present information from the boxed warning on the potentially fatal risks associated with OxyContin and its abuse liability, along with omitting important information about the limitations on the indicated use of OxyContin.[38] The FDA requested that Purdue cease disseminating these advertisements and any similar violative materials and provide a plan of corrective action. In response, Purdue issued a corrected advertisement, which called attention to the warning letter and the cited violations and directed the reader to the prominently featured boxed warning and indication information for OxyContin.[39] The FDA letter was one of only four warning letters issued to drug manufacturers during the first 8 months of 2003.[40]

In addition, in follow-up discussions with Purdue officials on the January 2003 warning letter, FDA expressed concerns about some of the information on Purdue's "Partners Against Pain" Web site. The Web site appeared to suggest unapproved uses of OxyContin for postoperative pain that may have been inconsistent with OxyContin's labeling and lacked risk

[36]FDA indicated that in 2000, it issued 75 untitled letters to 46 drug manufacturers, as well as 4 warning letters to 4 drug manufacturers, for using promotional activities that violated the FD&C Act.

[37]The advertisement appeared in the *New England Journal of Medicine* in May 2000.

[38]The advertisements appeared in the *Journal of the American Medical Association* in October and November 2002.

[39]According to FDA, the corrective advertisement ran for 3 months and appeared in approximately 30 medical journals.

[40]FDA indicated that from January through August 2003, it issued 4 warning letters to four manufacturers and 12 untitled letters to seven drug manufacturers for using promotional activities that violated the FD&C Act.

information about the drug. For example, one section of the Web site did not disclose that OxyContin is not indicated for pain in the immediate postoperative period—the first 12 to 24 hours following surgery—for patients not previously taking the drug, because its safety in this setting has not been established. The Web site also did not disclose that OxyContin is indicated for postoperative pain in patients already taking the drug or for use after the first 24 hours following surgery only if the pain is moderate to severe and expected to persist for an extended period of time. Purdue voluntarily removed all sections of the Web site that were of concern to FDA.

FDA has also sent enforcement letters to other manufacturers of controlled substances for marketing and promotion violations of the FD&C Act. For example, in 1996, FDA issued an untitled letter to Zeneca Pharmaceuticals, at the time the promoter of Kadian,[41] for providing information about the drug to a health professional prior to its approval in the United States. Roxane Laboratories, the manufacturer of Oramorph SR, was issued four untitled letters between 1993 and 1995 for making misleading and possibly false statements. Roxane used children in an advertisement even though Oramorph SR had not been evaluated in children, and a Roxane sales representative issued a promotional letter to a pharmacist that claimed, among other things, that Oramorph SR was superior to MS Contin in providing pain relief. FDA has sent no enforcement letters to Ligand Pharmaceuticals concerning Avinza.

Purdue Distributed an OxyContin Video without FDA's Review That Appears to Have Made Unsubstantiated Claims and Minimized Risks

Beginning in 1998, Purdue, as part of its marketing and promotion of OxyContin, distributed 15,000 copies of an OxyContin video to physicians without submitting it to FDA for review. This video, entitled *I Got My Life Back: Patients in Pain Tell Their Story*, presented the pain relief experiences of various patients and the pain medications, including OxyContin, they had been prescribed. FDA regulations require pharmaceutical manufacturers to submit all promotional materials for approved prescription drug products to the agency at the time of their initial use. Because Purdue did not comply with this regulation, FDA did not have an opportunity to review the video to ensure that the information it contained was truthful, balanced, and accurately communicated. Purdue has acknowledged the oversight of not submitting the video to FDA for

[41]Zeneca Pharmaceuticals promoted Kadian for Faulding Laboratories, the drug's manufacturer at that time.

review. In February 2001, Purdue submitted a second version of the video to FDA, which included information about the 160-milligram OxyContin tablet. FDA did not review this second version until October 2002, after we inquired about its content. FDA told us it found that the second version of the video appeared to make unsubstantiated claims regarding OxyContin's effect on patients' quality of life and ability to perform daily activities and minimized the risks associated with the drug.

The 1998 video used a physician spokesperson to describe patients with different pain syndromes and the limitations that each patient faced in his or her daily activities. Each patient's pain treatment was discussed, along with the dose amounts and brand names of the prescription drugs, including OxyContin, that either had been prescribed in the past or were being prescribed at that time. The physician in the videos also stated that opioid analgesics have been shown to cause addiction in less than 1 percent of patients—a fact that FDA has stated has not been substantiated. At the end of the video, the OxyContin label was scrolled for the viewer.

In 2000, Purdue submitted another promotional video to FDA entitled *I Got My Life Back: A Two Year Follow up of Patients in Pain*, and it submitted a second version of this video in 2001, which also included information on the 160-milligram OxyContin tablet. Purdue distributed 12,000 copies of these videos to physicians. Both versions scrolled the OxyContin label at the end of the videos. FDA stated that it did not review either of these videos for enforcement purposes because of limited resources. Distribution of all four Purdue videos was discontinued by July 2001, in response to OxyContin's labeling changes, which required the company to modify all of its promotional materials, but copies of the videos that had already been distributed were not retrieved and destroyed.

FDA said that it receives numerous marketing and promotional materials for promoted prescription drugs and that while every effort is made to review the materials, it cannot guarantee that all materials are reviewed because of limited resources and competing priorities. FDA officials also stated that pharmaceutical companies do not always submit promotional materials as required by regulations and that in such instances FDA would not have a record of the promotional pieces.

Several Factors May Have Contributed to OxyContin Abuse and Diversion, but Relationship to Availability Cannot Be Assessed

There are several factors that may have contributed to the abuse and diversion of OxyContin. OxyContin's formulation as a controlled-release opioid that is twice as potent as morphine may have made it an attractive target for abuse and diversion. In addition, the original label's safety warning advising patients not to crush the tablets because of the possible rapid release of a potentially toxic amount of oxycodone may have inadvertently alerted abusers to possible methods for misuse. Further, the rapid growth in OxyContin sales increased the drug's availability in the marketplace and may have contributed to opportunities to obtain the drug illicitly. The history of abuse and diversion of prescription drugs in some geographic areas, such as those within the Appalachian region, may have predisposed some states to problems with OxyContin. However, we could not assess the relationship between the growth in OxyContin prescriptions or increased availability with the drug's abuse and diversion because the data on abuse and diversion are not reliable, comprehensive, or timely.

OxyContin's Formulation May Have Made It an Inviting Drug for Abuse and Diversion

While OxyContin's potency and controlled-release feature may have made the drug beneficial for the relief of moderate-to-severe pain over an extended period of time, DEA has stated that those attributes of its formulation have also made it an attractive target for abuse and diversion. According to recent studies, oxycodone, the active ingredient in OxyContin, is twice as potent as morphine.[42] In addition, OxyContin's controlled-release feature allows a tablet to contain more active ingredient than other, non-controlled-release oxycodone-containing drugs.

One factor that may have contributed to the abuse and diversion of OxyContin was FDA's original decision to label the drug as having less abuse potential than other oxycodone products because of its controlled-release formulation. FDA officials said when OxyContin was approved the agency believed that the controlled-release formulation would result in less abuse potential because, when taken properly, the drug would be absorbed slowly, without an immediate rush or high. FDA officials acknowledged that the initial wording of OxyContin's label was "unfortunate" but was based on what was known about the product at that time.

[42]See, for example, G.B. Curtis, et al. "Relative Potency of Controlled-Release Oxycodone and Morphine in a Postoperative Pain Model," *European Journal of Clinical Pharmacology*, vol. 55, no. 6 (1999): 55:425-429.

FDA officials told us that abusers typically seek a drug that is intense and fast-acting. When OxyContin was approved, FDA did not recognize that if the drug is dissolved in water and injected its controlled-release characteristics could be disrupted, creating an immediate rush or high and thereby increasing the potential for misuse and abuse. DEA officials told us that OxyContin became a target for abusers and diverters because the tablet contained larger amounts of active ingredient and the controlled-release formulation was easy for abusers to compromise.

The safety warning on the OxyContin label may also have contributed to the drug's potential for abuse and diversion, by inadvertently providing abusers with information on how the drug could be misused. The label included the warning that the tablets should not be broken, chewed, or crushed because such action could result in the rapid release and absorption of a potentially toxic dose of oxycodone. FDA places similar safety warnings on other drugs to ensure that they are used properly. FDA officials stated that neither they nor other experts anticipated that crushing the controlled-release tablet and intravenously injecting or snorting the drug would become widespread and lead to a high level of abuse.

OxyContin's Wide Availability May Have Increased Opportunities for Illicit Use

The large amount of OxyContin available in the marketplace may have increased opportunities for abuse and diversion. Both DEA and Purdue have stated that an increase in a drug's availability in the marketplace may be a factor that attracts interest by those who abuse and divert drugs. Following its market introduction in 1996, OxyContin sales and prescriptions grew rapidly through 2002. In 2001 and 2002 combined, sales of OxyContin approached $3 billion, and over 14 million prescriptions for the drug were dispensed. (See table 2.) OxyContin also became the top-selling brand-name narcotic pain reliever in 2001 and was ranked 15th on a list of the nation's top 50 prescription drugs by retail sales.[43]

[43]This information is from the National Institute for Health Care Management's Prescription Drug Expenditures reports for 2000 and 2001, prepared using American Institutes for Research analysis of Scott-Levin Prescription Audit Data. OxyContin was ranked 18th in 2000.

Table 2: Total OxyContin Sales and Prescriptions for 1996 through 2002 with Percentage Increases from Year to Year

Year	Sales	Percentage increase	Number of prescriptions	Percentage increase
1996	$44,790,000	N/A	316,786	N/A
1997	125,464,000	180	924,375	192
1998	286,486,000	128	1,910,944	107
1999	555,239,000	94	3,504,827	83
2000	981,643,000	77	5,932,981	69
2001	1,354,717,000	38	7,183,327	21
2002	1,536,816,000	13	7,234,204	7

Sources: Purdue and IMS Health.

Legend: N/A = not applicable.

Note: GAO analysis of OxyContin sales and prescription data from Purdue and IMS Health, which includes data from all 50 states and the District of Columbia. Sales include combined retail and nonretail sales in drugstores, hospitals, and long-term-care facilities from the IMS Health U.S. National Sales database. Prescriptions include retail pharmacy, long-term-care, and mail-order prescriptions from IMS Health's National Prescriptions Audit.

History of Prescription Drug Abuse in Some States May Have Predisposed Them to Problems with OxyContin

According to DEA, the abuse and diversion of OxyContin in some states may have reflected the geographic area's history of prescription drug abuse. The White House Office of National Drug Control Policy (ONDCP) designates geographic areas with illegal drug trade activities for allocation of federal resources to link local, state, and federal drug investigation and enforcement efforts. These areas, known as High-Intensity Drug Trafficking Areas (HIDTA), are designated by ONDCP in consultation with the Attorney General, the Secretary of the Treasury, heads of drug control agencies, and governors in the states involved.[44]

According to a 2001 HIDTA report,[45] the Appalachian region, which encompasses parts of Kentucky, Tennessee, Virginia, and West Virginia,

[44]In making a designation, ONDCP considers whether the geographic area is a center of drug production, manufacturing, importation, or distribution; whether state and local law enforcement agencies have committed resources to respond aggressively to the drug trafficking problem; whether drug activities in the area are having a harmful impact on other areas of the country; and whether a significant increase in federal resources is necessary to respond to the area's drug-related activities.

[45]Appalachia High Intensity Drug Trafficking Area Task Force, *The OxyContin Threat in Appalachia* (London, Ky.: August 2001).

has been severely affected by prescription drug abuse, particularly pain relievers, including oxycodone, for many years. Three of the four states—Kentucky, Virginia, and West Virginia—were among the initial states to report OxyContin abuse and diversion. Historically, oxycodone, manufactured under brand names such as Percocet, Percodan, and Tylox, was among the most diverted prescription drugs in Appalachia. According to the report, OxyContin has become the drug of choice of abusers in several areas within the region. The report indicates that many areas of the Appalachian region are rural and poverty-stricken, and the profit potential resulting from the illicit sale of OxyContin may have contributed to its diversion and abuse. In some parts of Kentucky, a 20-milligram OxyContin tablet, which can be purchased by legitimate patients for about $2, can be sold illicitly for as much as $25. The potential to supplement their incomes can lure legitimate patients into selling some of their OxyContin to street dealers, according to the HIDTA report.

Limitations on Abuse and Diversion Data Prevent Assessment of the Relationship with OxyContin's Availability

The databases DEA uses to track the abuse and diversion of controlled substances all have limitations that prevent an assessment of the relationship between the availability of OxyContin and areas where the drug is being abused or diverted. Specifically, these databases, which generally do not provide information on specific brand-name drugs such as OxyContin, are based on data gathered from limited sources in specific geographic areas and have a significant time lag. As a result, they do not provide reliable, complete, or timely information that could be used to identify abuse and diversion of a specific drug.

DEA officials told us that it is difficult to obtain reliable data on what controlled substances are being abused by individuals and diverted from pharmacies because available drug abuse and diversion tracking systems do not capture data on a specific brand-name product or indicate where a drug product is being abused and diverted on a state and local level. Because of the time lags in reporting information, the data reflect a delayed response to any emerging drug abuse and diversion problem. For example, the Drug Abuse Warning Network (DAWN) estimates national drug-related emergency department visits or deaths involving abused drugs using data collected by the Substance Abuse and Mental Health Services Administration (SAMHSA). The data are collected from hospital emergency departments in 21 metropolitan areas that have agreed to voluntarily report drug-abuse-related information from a sample of patient

medical records, and from medical examiners in 42 metropolitan areas.[46] However, DAWN cannot make estimates for rural areas, where initial OxyContin abuse and diversion problems were reported to be most prevalent, nor does it usually provide drug-product-specific information, and its data have a lag time of about 1 year. DEA stated that development of enhanced data collection systems is needed to provide "credible, legally defensible evidence concerning drug abuse trends in America."[47]

DEA relies primarily on reports from its field offices to determine where abuse and diversion are occurring. DEA officials stated that the initial areas that experienced OxyContin abuse and diversion problems included rural areas within 8 states—Alaska, Kentucky, Maine, Maryland, Ohio, Pennsylvania, Virginia, and West Virginia. In July 2002, DEA told us that it learned that OxyContin abuse and diversion problems had spread into larger areas of the initial 8 states, as well as parts of 15 other states, to involve almost half of the 50 states.[48] According to DEA officials, while DEA field offices continue to report OxyContin as a drug of choice among abusers, OxyContin has not been and is not now considered the most highly abused and diverted prescription drug nationally.[49] OxyContin is the most abused single-entity prescription product according to those DEA state and divisional offices that report OxyContin abuse.

[46]The reliability of the data collected depends on whether the emergency room patient visit was reported as drug related, whether the patient reported taking a particular drug, and whether the emergency room physician indicated a drug's brand name in the patient's medical record.

[47]See app. III for more details on the abuse and diversion databases DEA uses.

[48]The 15 states are Alabama, Arizona, Colorado, Connecticut, Florida, Louisiana, Massachusetts, Mississippi, Missouri, New Jersey, North Carolina, South Carolina, Texas, Washington, and Wisconsin.

[49]Hydrocodone products, such as Anexsia, Hycodan, Lorcet, Lortab, and Vicodin, remain among the most abused and diverted scheduled prescription drugs nationally.

Federal and State Agencies and Purdue Have Taken Actions to Prevent Abuse and Diversion of OxyContin

Since becoming aware of reports of abuse and diversion of OxyContin, federal and state agencies and Purdue have taken actions intended to address these problems. To protect the public health, FDA has strengthened OxyContin label warnings and requested that Purdue develop and implement an OxyContin risk management plan. In addition, DEA has stepped up law enforcement actions to prevent abuse and diversion of OxyContin. State Medicaid fraud control units have also attempted to identify those involved in the abuse and diversion of OxyContin. Purdue has initiated drug abuse and diversion education programs, taken disciplinary actions against sales representatives who improperly promote OxyContin, and referred physicians who were suspected of improperly prescribing OxyContin to the appropriate authorities. However, until fall 2002 Purdue did not analyze its comprehensive physician prescribing reports, which it routinely uses in marketing and promoting OxyContin, and other indicators to identify possible physician abuse and diversion.

Reports of Abuse and Diversion Led to Label Changes and Other Actions by FDA

Reports of abuse and diversion of OxyContin that were associated with an increasing incidence of addiction, overdose, and death prompted FDA to revise the drug's label and take other actions to protect the public health. In July 2001, FDA reevaluated OxyContin's label and made several changes in an effort to strengthen the "Warnings" section of the label. FDA added a subsection—"Misuse, Abuse, and Diversion of Opioids"—to stress that physicians and pharmacists should be alert to the risk of misuse, abuse, and diversion when prescribing or dispensing OxyContin. FDA also added a black box warning—the highest level of warning FDA can place on an approved drug product. FDA highlighted the language from the original 1995 label—stating that OxyContin is a schedule II controlled substance with an abuse liability similar to morphine—by moving it into the black box. Also, while the original label suggested that taking broken, chewed, or crushed OxyContin tablets "could lead to the rapid release and absorption of a potentially toxic dose of oxycodone," a more strongly worded warning in the black box stated that taking the drug in this manner "*leads* to rapid release and absorption of a potentially *fatal* dose of oxycodone" (emphasis added). (See table 3.) In addition to the black box warning, FDA also changed the language in the original label that described the incidence of addiction inadvertently induced by physician prescribing as rare if opioids are legitimately used in the management of pain. The revised label stated that data are not available to "establish the true incidence of addiction in chronic patients."

Table 3: Selected Language Approved by FDA in Warning Sections of OxyContin Labels, 1995 and 2001

Warning label in 1995	Black box warning in 2001
"Warning: OxyContin Tablets are to be swallowed whole, and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed OxyContin Tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone."	"Warning: OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine." "OxyContin Tablets are to be swallowed whole and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed OxyContin Tablets **leads** to rapid release and absorption of a potentially **fatal** dose of oxycodone." (emphasis added)

Source: FDA-approved label for Purdue's OxyContin.

As mentioned earlier, the indication described in the original label was also revised to clarify the appropriate time period for which OxyContin should be prescribed for patients experiencing moderate-to-severe pain. The language in the 1995 label was changed from "where use of an opioid analgesic is appropriate for more than a few days" to "when a continuous, around-the-clock analgesic is needed for an extended period of time." (See table 4.) A summary of changes made by FDA to the original OxyContin label is given in appendix II.

Table 4: Selected Language Approved by FDA in the Indication Sections of OxyContin Labels, 1995 and 2001

Indication in 1995	Black box indication change in 2001
"OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate-to-severe pain where use of an opioid analgesic is appropriate for more than a few days."	"OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate-to-severe pain **when a continuous, around-the-clock analgesic is needed for an extended period of time**." (emphasis added)

Source: FDA-approved label for Purdue's OxyContin.

Beginning in early 2001, FDA collaborated with Purdue to develop and implement a risk management plan to help identify and prevent abuse and diversion of OxyContin. As a part of the risk management plan in connection with the labeling changes, Purdue was asked by FDA to revise all of its promotional materials for OxyContin to reflect the labeling

changes. In August 2001, FDA sent a letter to Purdue stating that all future promotional materials for OxyContin should prominently disclose the information contained in the boxed warning; the new warnings that address misuse, abuse, diversion, and addiction; and the new precautions and revised indication for OxyContin. Purdue agreed to comply with this request.

FDA officials told us that it is standard procedure to contact a drug manufacturer when the agency becomes aware of reports of abuse and diversion of a drug product so that FDA and the drug manufacturer can tailor a specific response to the problem. While FDA's experience with risk management plans is relatively new, agency officials told us that OxyContin provided the opportunity to explore the use of the plans to help identify abuse and diversion problems. FDA is currently making decisions about whether risk management plans will be requested for selected opioid products. Also, in September 2003, FDA's Anesthetic and Life Support Drugs Advisory Committee held a public hearing to discuss its current review of proposed risk management plans for opioid analgesic drug products to develop strategies for providing patients with access to pain treatment while limiting the abuse and diversion of these products.

FDA has also taken other actions to address the abuse and diversion of OxyContin. It put information on its Web site for patients regarding the appropriate use of OxyContin.[50] FDA worked with Purdue to develop "Dear Health Care Professional" letters, which the company distributed widely to health care professionals to alert them that the package insert had been revised to clarify the indication and strengthen the warnings related to misuse, abuse, and diversion. FDA also has worked with DEA, SAMHSA, the National Institute on Drug Abuse, ONDCP, and the Centers for Disease Control and Prevention to share information and insights on the problem of abuse and diversion of OxyContin.

DEA Developed an Action Plan to Deter OxyContin Abuse and Diversion

In April 2001, DEA developed a national action plan to deter abuse and diversion of OxyContin. According to DEA officials, this marked the first time the agency had targeted a specific brand-name product for monitoring because of the level and frequency of abuse and diversion associated with the drug. Key components of the action plan include coordinating enforcement and intelligence operations with other law

[50]See www.fda.gov/cder/drug/infopage/oxycontin/default.htm.

enforcement agencies to target people and organizations involved in abuse and diversion of OxyContin, pursuing regulatory and administrative action to limit abusers' access to OxyContin, and building national outreach efforts to educate the public on the dangers related to the abuse and diversion of OxyContin. DEA has also set Purdue's procurement quota for oxycodone at levels lower than the levels requested by Purdue.

DEA has increased enforcement efforts to prevent abuse and diversion of OxyContin. From fiscal year 1996 through fiscal year 2002, DEA initiated 313 investigations involving OxyContin, resulting in 401 arrests. Most of the investigations and arrests occurred after the initiation of the action plan. Since the plan was enacted, DEA initiated 257 investigations and made 302 arrests in fiscal years 2001 and 2002. Among those arrested were several physicians and pharmacists. Fifteen health care professionals either voluntarily surrendered their controlled substance registrations or were immediately suspended from registration by DEA. In addition, DEA reported that $1,077,500 in fines was assessed and $742,678 in cash was seized by law enforcement agencies in OxyContin-related cases in 2001 and 2002.

Among several regulatory and administrative actions taken to limit abusers' access to OxyContin and controlled substances, DEA's Office of Diversion Control, in collaboration with the Department of Justice's Office of Justice Programs, Bureau of Justice Assistance, provides grants to states for the establishment of prescription drug monitoring programs. The conference committee report for the fiscal year 2002 appropriation to the Department of Justice directed the Office of Justice Programs to make a $2 million grant in support of the Harold Rogers Prescription Drug Monitoring Program, which enhances the capacity of regulatory and law enforcement agencies to collect and analyze controlled substance prescription data. The program provided grants to establish new monitoring programs in Ohio, Pennsylvania, Virginia, and West Virginia. California, Kentucky, Massachusetts, Nevada, and Utah also received grants to enhance existing monitoring programs.

DEA has also attempted to raise national awareness of the dangers associated with abuse and diversion of OxyContin. In October 2001 DEA joined 21 national pain and health organizations in issuing a consensus statement calling for a balanced policy on prescription medication use. According to the statement, such a policy would acknowledge that health care professionals and DEA share responsibility for ensuring that prescription medications, such as OxyContin, are available to patients who need them and for preventing these drugs from becoming a source of

abuse and diversion. DEA and the health organizations also called for a renewed focus on educating health professionals, law enforcement, and the public about the appropriate use of opioid pain medications in order to promote responsible prescribing and limit instances of abuse and diversion. DEA is also working with FDA to encourage state medical boards to require, as a condition of their state licensing, that physicians obtain continuing medical education on pain management.

When OxyContin was first introduced to the market in 1996, DEA granted Purdue's initial procurement quota request for oxycodone. According to DEA, increases in the quota were granted for the first several years. Subsequently, concern over the dramatic increases in sales caused DEA to request additional information to support Purdue's requests to increase the quota. In the last several years, DEA has taken the additional step of lowering the procurement quota requested by Purdue for the manufacture of OxyContin as a means for addressing abuse and diversion. However, DEA has cited the difficulty of determining an appropriate level while ensuring that adequate quantities were available for legitimate medical use, as there are no direct measures available to establish legitimate medical need.

State Agencies Have Responded to Reports of OxyContin Abuse and Diversion

State Medicaid fraud control units and medical licensure boards have taken action in response to reports of abuse and diversion of OxyContin. State Medicaid fraud control units have conducted investigations of abuse and diversion of OxyContin, but generally do not maintain precise data on the number of investigations and enforcement actions completed. Although complete information was not available from directors of state Medicaid fraud control units in Kentucky, Maryland, Pennsylvania, Virginia, and West Virginia with whom we spoke, each of those directors told us that abuse and diversion of OxyContin is a problem in his or her state. The directors told us that they had investigated cases that involved physicians or individuals who had either been indicted or prosecuted for writing medically unnecessary OxyContin prescriptions in exchange for cash or sexual relationships.

State medical licensure boards have also responded to complaints about physicians who were suspected of abuse and diversion of controlled substances, but like the Medicaid fraud control units, the boards generally do not maintain data on the number of investigations that involved OxyContin. Representatives of state boards of medicine in Kentucky, Pennsylvania, Virginia, and West Virginia told us that they have received complaints from various sources, such as government agencies, health

care professionals, and anonymous tipsters, about physicians suspected of abuse and diversion of controlled substances. However, each of the four representatives stated that his or her board does not track the complaints by specific drug type and consequently cannot determine whether the complaints received allege physicians' misuse of OxyContin. Each of the four representatives also told us that his or her medical licensure board has adopted or strengthened guidelines or regulations for physicians on prescribing, administering, and dispensing controlled substances in the treatment of chronic pain. For example, in March 2001, the Kentucky Board of Medical Licensure adopted guidelines to clarify the board's position on the use of controlled substances for nonterminal/nonmalignant chronic pain.[51] The boards of medicine in Pennsylvania, Virginia, and West Virginia each have guidelines for the appropriate use of controlled substances that are similar to those adopted by Kentucky.

Purdue Is Implementing a Risk Management Plan for OxyContin

In response to concerns about abuse and diversion of OxyContin, in April 2001 FDA and Purdue began to discuss the development of a risk management plan to help detect and prevent abuse and diversion of OxyContin. Purdue submitted its risk management plan to FDA for review in August 2001.[52] The plan includes some actions that Purdue proposed to take, as well as others that it has already taken. Purdue's risk management plan includes actions such as strengthening the safety warnings on OxyContin's label for professionals and patients, training Purdue's sales force on the revised label, conducting comprehensive education programs for health care professionals, and developing a database for identifying and monitoring abuse and diversion of OxyContin.

Under the risk management plan, OxyContin's label was strengthened, effective in July 2001, by revising the physician prescribing information and adding a black box warning to call attention to OxyContin's potential

[51]The Kentucky guidelines for the use of controlled substances in pain treatment provide that (1) a complete medical history and examination be conducted and documented in patient medical records, (2) a written treatment plan state objectives for determining treatment success, (3) the risks and benefits of the use of controlled substances be discussed by physician and patient, (4) periodic review of the course of treatment be conducted, (5) consultation or referral to an expert in pain management be considered for patients who are at risk for substance abuse, (6) patient's medical record be kept accurate and complete, and (7) physicians be in compliance with applicable federal and state controlled substance laws and regulations.

[52]Amended versions of Purdue's risk management plan for OxyContin were submitted to FDA for review in April 2002 and in March 2003.

for misuse, abuse, and diversion. (See app. II.) Purdue trained its sales force on the specifics of the revised label and provided sales representatives with updated information on the appropriate use of opioid analgesics, legal guidelines associated with promotion of its products, and their responsibility and role in reporting adverse events. Purdue also reiterated to its sales representatives that failure to promote products according to the approved label, promotional materials, and applicable FDA standards would result in disciplinary action by the company. According to Purdue, from April 2001 through May 2003 at least 10 Purdue employees were disciplined for using unapproved materials in promoting OxyContin. Disciplinary actions included warning letters, suspension without pay, and termination.

Purdue also has provided education programs for health care professionals and the public under its risk management plan. For example, in 2001 Purdue supported seminars that examined ways health care professionals can help prevent abuse and diversion of opioids. Purdue worked with DEA and other law enforcement agencies to develop and implement antidiversion educational programs. In 2002, Purdue also launched the Web site painfullyobvious.com to educate teenagers, parents, law enforcement officers, and discussion leaders about the dangers of prescription drug abuse.

Because reliable data on the abuse and diversion of controlled substance drugs are not available, Purdue developed the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System, as part of its risk management plan, to study the nature and extent of abuse of OxyContin and other schedule II and III prescription medications and to implement interventions to reduce abuse and diversion.[53] According to Purdue, RADARS collects and computes abuse, diversion, and addiction rates for certain drugs based on population and determines national and local trends.

Since the launch of OxyContin, Purdue has provided its sales force with considerable information to help target physicians and prioritize sales contacts within a sales territory. Sales representatives routinely receive daily, weekly, monthly, and quarterly physician prescribing reports based

[53]RADARS will collect information on brand-name and generic versions of buprenorphine, fentanyl, hydrocodone, hydromorphone, oxycodone, morphine, and methadone. Benzodiazepine is scheduled to be added to RADARS in late 2003.

on IMS Health data that specify the physicians who have written prescriptions for OxyContin and other opioid analgesics, and the number of prescriptions written. Although this information has always been available for use by Purdue and its sales representatives, it was not until fall 2002 that Purdue directed its sales representatives to begin using 11 indicators to identify possible abuse and diversion and to report the incidents to Purdue's General Counsel's Office for investigation. Among the possible indicators are a sudden unexplained change in a physician's prescribing patterns that is not accounted for by changes in patient numbers, information from credible sources such as a pharmacist that a physician or his or her patients are diverting medications, or a physician who writes a large number of prescriptions for patients who pay with cash. As of September 2003, Purdue—through its own investigations—had identified 39 physicians and other health care professionals who were referred to legal, medical, or regulatory authorities for further action. Most of the 39 referrals stemmed from reports by Purdue's sales force.

Other actions included in the plan that were taken by Purdue prior to submission of its risk management plan include discontinuance of the 160-milligram tablet of OxyContin to reduce the risk of overdose from this dosage strength, the development of unique markings for OxyContin tablets intended for distribution in Mexico and Canada to assist law enforcement in identifying OxyContin illegally smuggled into the United States, and the distribution of free tamper-resistant prescription pads designed to prevent altering or copying of the prescription. Purdue also implemented a program in 2001 to attempt to predict "hot spots" where OxyContin abuse and diversion were likely to occur, but discontinued the program in 2002 when Purdue concluded that nearly two-thirds of the counties identified had no abuse and diversion.

Conclusions

At present, both federal agencies and the states have responsibilities involving prescription drugs and their abuse and diversion. FDA is responsible for approving new drugs and ensuring that the materials drug companies use to market and promote these drugs are truthful, balanced, and accurate. However, FDA examines these promotional materials only after they have been used in the marketplace because the FD&C Act generally does not give FDA authority to review these materials before the drug companies use them. Moreover, the FD&C Act provisions governing drug approval and promotional materials make no distinction between controlled substances, such as OxyContin, and other prescription drugs. DEA is responsible for registering handlers of controlled substances, approving production quotas and monitoring distribution of controlled

substances to the retail level. It is the states, however, that are responsible for overseeing the practice of medicine and pharmacy where drugs are prescribed and dispensed. Some states have established prescription drug monitoring programs to help them detect and deter abuse and diversion. However, these programs exist in only 15 states and most do not proactively analyze prescription data to identify individuals, physicians, or pharmacies that have unusual use, prescribing, or dispensing patterns that may suggest potential drug diversion or abuse.

The significant growth in the use of OxyContin to treat patients suffering from chronic pain has been accompanied by widespread reports of abuse and diversion that have in some cases led to deaths. The problem of abuse and diversion has highlighted shortcomings at the time of approval in the labeling of schedule II controlled substances, such as OxyContin, and in the plans in place to detect misuse, as well as in the infrastructure for detecting and preventing the abuse and diversion of schedule II controlled substances already on the market.

Addressing abuse and diversion problems requires the collaborative efforts of pharmaceutical manufacturers; the federal and state agencies that oversee the approval and use of prescription drugs, particularly controlled substances; the health care providers who prescribe and dispense them; and law enforcement. After the problems with OxyContin began to surface, FDA and Purdue collaborated on a risk management plan to help detect and prevent abuse and diversion. Although risk management plans were not in use when OxyContin was approved, they are now an optional feature of new drug applications. FDA plans to complete its guidance to the pharmaceutical industry on risk management plans by September 30, 2004. The development of this guidance, coupled with FDA's current review of proposed risk management plans for modified-release opioid analgesics, provides an opportunity to help ensure that manufacturers include a strategy to monitor the use of these drugs and to identify potential problems with abuse and diversion.

Recommendation for Executive Action

To improve efforts to prevent or identify the abuse and diversion of schedule II controlled substances, we recommend that the Commissioner of Food and Drugs ensure that FDA's risk management plan guidance encourages pharmaceutical manufacturers that submit new drug applications for these substances to include plans that contain a strategy for monitoring the use of these drugs and identifying potential abuse and diversion problems.

Agency and Purdue Comments and Our Evaluation

We provided a draft of this report to FDA, DEA, and Purdue, the manufacturer of OxyContin, for their review. FDA and DEA provided written comments. (See apps. IV and V.) Purdue's representatives provided oral comments.

FDA said that it agreed with our recommendation that its risk management plan guidance should encourage all pharmaceutical manufacturers submitting new drug applications for schedule II controlled substances to include strategies to address abuse and diversion concerns. FDA stated that the agency is working on the risk management plan guidance. FDA also noted that the FD&C Act makes no distinction between controlled substances and other prescription drugs in its provisions regulating promotion, but that as a matter of general policy, the agency more closely scrutinizes promotion of drugs with more serious risk profiles. However, FDA does not have written guidance that specifies that promotional materials for controlled substances receive priority or special attention over similar materials for other prescription drugs. Furthermore, our finding that FDA did not review any of the OxyContin promotional videos provided by Purdue until we brought them to the agency's attention raises questions about whether FDA provides extra attention to promotional materials for controlled substances that by definition have a high potential for abuse and may lead to severe psychological or physical dependence. FDA recommended that we clarify our description of the content of the warning letter issued to Purdue and provide additional information describing the extent of the corrective action taken by Purdue. FDA also recommended noting in the report that part of the risk management plan in connection with the 2001 labeling changes was a requirement that all OxyContin promotional materials be revised to reflect the labeling changes and all future materials prominently disclose this information. Finally, FDA noted that the promotional videos discussed in the report were submitted by Purdue prior to the labeling change and discontinued as a result of the labeling change. As we note in the report, Purdue acknowledged that all the promotional videos were not submitted to FDA at the time they were distributed. Moreover, although Purdue told us that these videos were no longer distributed after the label change, those videos that had been distributed were not collected and destroyed. We revised the report to reflect FDA's general comments. FDA also provided technical comments that we incorporated where appropriate.

In its written comments, DEA agreed that the data on abuse and diversion are not reliable, comprehensive, or timely, as we reported. DEA reiterated its previous statement that Purdue's aggressive marketing of OxyContin fueled demand for the drug and exacerbated the drug's abuse and

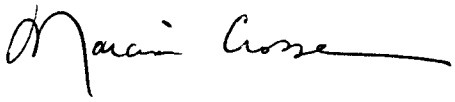
diversion. DEA also stated that Purdue minimized the abuse risk associated with OxyContin. We agree with DEA that Purdue conducted an extensive campaign to market and promote OxyContin using an expanded sales force and multiple promotional approaches to encourage physicians, including primary care specialists, to prescribe OxyContin as an initial opioid treatment for noncancer pain, and that these efforts may have contributed to the problems with abuse and diversion by increasing the availability of the drug in the marketplace. However, we also noted that other factors may have contributed to these problems. We also agree that Purdue marketed OxyContin as having a low abuse liability, but we noted that this was based on information in the original label approved by FDA. DEA also acknowledged that the lack of a real measure of legitimate medical need for a specific product (OxyContin), substance (oxycodone), or even a class of substances (controlled release opioid analgesics) makes it difficult to limit manufacturing as a means of deterring abuse and diversion. DEA also noted that it is essential that risk management plans be put in place prior to the introduction of controlled substances into the marketplace, consistent with our recommendation. We revised the report to provide some additional detail on problems associated with OxyContin and Purdue's marketing efforts. DEA provided some technical comments on the draft report that we incorporated where appropriate.

Purdue representatives provided oral comments on a draft of this report. In general, they thought the report was fair and balanced; however, they offered both general and technical comments. Specifically, Purdue stated that the report should add the media as a factor contributing to the abuse and diversion of OxyContin because media stories provided the public with information on how to "get high" from using OxyContin incorrectly. Our report notes that the safety warning on the original label may have inadvertently alerted abusers to a possible method for misusing the drug. However, we note that the original label was publicly available from FDA once OxyContin was approved for marketing. Purdue also suggested that we include Duragesic, also a schedule II opioid analgesic, as a fourth comparable drug to OxyContin. The three comparable drugs we used in the report were chosen in consultation with FDA as comparable opioid analgesics to OxyContin, because they were time-released, morphine-based schedule II drugs formulated as tablets like OxyContin. In contrast, Duragesic, which contains the opioid analgesic fentanyl and provides pain relief over a 72-hour period, is formulated as a skin patch to be worn rather than as a tablet. Purdue representatives also provided technical comments that were incorporated where appropriate.

We also provided sections of this draft report to the manufacturers of three comparative drugs we examined. Two of the three companies with a drug product used as a comparable drug to OxyContin reviewed the portions of the draft report concerning their own product, and provided technical comments, which were incorporated where appropriate. The third company did not respond to our request for comments.

As agreed with your offices, unless you publicly announce this report's contents earlier, we plan no further distribution until 30 days after its issue date. At that time, we will send copies of this report to the Commissioner of Food and Drugs, the Administrator of the Drug Enforcement Administration, Purdue, and the other pharmaceutical companies whose drugs we examined. We will also make copies available to others upon request. In addition, the report will be available at no charge on the GAO Web site at http://www.gao.gov.

If you or your staffs have any questions about this report, please call me at (202) 512-7119 or John Hansen at (202) 512-7105. Major contributors to this report were George Bogart, Darryl Joyce, Roseanne Price, and Opal Winebrenner.



Marcia Crosse
Director, Health Care—Public Health
and Military Health Care Issues

Appendix I: Scope and Methodology

To identify the strategies and approaches used by Purdue Pharma L.P. (Purdue) to market and promote OxyContin, we interviewed Purdue officials and analyzed company documents and data. Specifically, we interviewed Purdue officials concerning its marketing and promotional strategies for OxyContin, including its targeting of physicians with specific specialties and its sales compensation plan to provide sales representatives with incentives for the drug's sales. We also interviewed selected Purdue sales representatives who had high and midrange sales during 2001 from Kentucky, Pennsylvania, Virginia, and West Virginia—four states that were initially identified by the Drug Enforcement Agency (DEA) as having a high incidence of OxyContin drug abuse and diversion—and from California, Massachusetts, and New Jersey—three states that DEA did not initially identify as having problems with OxyContin. We asked the sales representatives about their training, promotional strategies and activities, and targeting of physicians. We also interviewed physicians who were among the highest prescribers of OxyContin regarding their experiences with Purdue sales representatives, including the strategies used to promote OxyContin, as well as their experiences with sales representatives of manufacturers of other opioid analgesics. We reviewed Purdue's quarterly action plans for marketing and promoting OxyContin for 1996 through 2003, Purdue's sales representative training materials, and materials from ongoing OxyContin-related litigation. To obtain information on how Purdue's marketing and promotion of OxyContin compared to that of other companies, we identified, in consultation with the Food and Drug Administration (FDA), three opioid analgesics that were similar to OxyContin. The three drugs—Avinza, Kadian, and Oramorph SR—are all time-released, morphine-based analgesics that are classified as schedule II controlled substances. We examined the promotional materials each drug's manufacturer submitted to FDA and any actions FDA had taken against the manufacturers related to how the drugs were marketed or promoted. We also interviewed company officials about how they marketed and promoted their respective drugs. Because of their concerns about proprietary information, the three companies did not provide us with the same level of detail about their drugs' marketing and promotion as did Purdue.

To examine factors that contributed to the abuse and diversion of OxyContin, we reviewed DEA abuse and diversion data as part of an effort to compare them with DEA's OxyContin state distribution data and with IMS Health data on the rates of OxyContin sales and prescription dispensing to determine if they occurred in similar geographic areas. We also analyzed the distribution of Purdue sales representatives by state and compared them with the availability of OxyContin and abuse and diversion

data to determine whether states with high rates of OxyContin sales and prescription dispensing and abuse and diversion problems had more sales representatives per capita than other states. However, limitations in the abuse and diversion data prevent an assessment of the relationship between the availability of OxyContin and areas where the drug was abused and diverted. We also reviewed the High Intensity Drug Trafficking Area (HIDTA) reports on states with histories of illegal drug activities. We interviewed DEA and FDA officials, physicians who prescribed OxyContin, officials from physician licensing boards in selected states, officials from national health practitioner groups, and company officials and sales representatives about why OxyContin abuse and diversion have occurred.

To determine the efforts federal and state agencies and Purdue have made to identify and prevent abuse and diversion of controlled substances such as OxyContin, we interviewed FDA officials and analyzed information from FDA regarding the marketing and promotion of controlled substances, specifically OxyContin; FDA's decision to approve the original label for OxyContin; and FDA's subsequent decision to revise OxyContin's labeling, as well as FDA's role in monitoring OxyContin's marketing and advertising activities. We also interviewed DEA officials about the agency's efforts to identify and prevent abuse and diversion, including its national action plan for OxyContin, and how it determines the prevalence of OxyContin abuse and diversion nationally. We also interviewed officials from national practitioner associations, Medicaid fraud control units, and physician licensing boards in states with initial reports of abuse and diversion—Kentucky, Maryland, Pennsylvania, Virginia, and West Virginia—regarding concerns they had about the abuse and diversion of OxyContin. We reviewed Purdue's OxyContin risk management plan submissions to FDA from 2001 through 2003 to identify actions taken by Purdue to address abuse and diversion of OxyContin.

Appendix II: Summary of FDA Changes to the Original Approved OxyContin Label

Table 5 provides a description of the changes made by FDA to sections of the original OxyContin approved label from June 1996 through July 2001. These changes included a black box warning, the strongest warning an FDA-approved drug can carry, and specifically addressed areas of concern related to the opioid characteristics of oxycodone and its risk of abuse and diversion.

Table 5: FDA Changes to the Original OxyContin Label Made from June 1996 through July 2001

Summary of FDA changes to original OxyContin label in 2001	Language in OxyContin label approved in 2001
Black box warning was added to stress the opioid nature of oxycodone and risks for abuse and diversion of the drug.	"**WARNING:** **OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.** Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. **OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.** OxyContin Tablets are NOT intended for use as a prn analgesic. OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. **These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids. OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE**."
Clinical pharmacology —Provides a pharmacological description of oxycodone as a pure opioid agonist whose principal action is analgesia. —Identifies other members of the opioid agonist class, such as morphine, hydromorphone, fentanyl, and hydrocodone. —Describes the pharmacological properties of opioids in general (anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia). —Describes respiratory depression as one of the most serious side effects of opioids that could lead to overdose or death.	"**CLINICAL PHARMACOLOGY** Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression."

Summary of FDA changes to original OxyContin label in 2001	Language in OxyContin label approved in 2001
Misuse, abuse, and diversion of opioids A subsection on misuse, abuse and diversion was added to the WARNINGS section of the label. —Characterizes oxycodone as an opioid agonist of the morphine-type and stresses that opioid agonists are sought by drug abusers and people with addiction disorders and are subject to diversion. —Makes clear that oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit, and that physicians and pharmacists should be aware of and alert to risk of misuse, abuse, and diversion when prescribing or dispensing oxycodone. —Modifies original label statement that iatrogenic addiction (addiction induced inadvertently by a physician or a physician's treatment) is rare if opioids were legitimately used in the management of pain to state that data are not available to establish the true incidence of addiction in chronic patients.	"**Misuse, Abuse and Diversion of Opioids** Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION).** Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse of this product."

Summary of FDA changes to original OxyContin label in 2001	Language in OxyContin label approved in 2001
Drug abuse and addiction —Emphasizes that the abuse potential of oxycodone is equivalent to that of morphine. —Describes the controlled status of OxyContin and emphasizes that, like morphine and other opioids used in analgesia, oxycodone can be abused and is subject to criminal diversion. —Stresses proper prescribing practices, dispensing, and storage. —Deletes statement that delayed absorption of OxyContin was believed to reduce the abuse liability of the drug. —Stresses the risks associated with parenteral injection of OxyContin and reiterates the original label's description of drug addiction and "drug-seeking" behaviors commonly in addicts and abusers.	"**DRUG ABUSE AND ADDICTION** **OxyContin is a mu-agonist with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.** Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin, like other opioids, has been diverted for non-medical use. Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs. **OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of enocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV**."
Safety and handling —Emphasizes the controlled status of OxyContin. —Alerts health care professionals that OxyContin could be a target for theft and diversion and instructs that they should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of the product.	"**SAFETY AND HANDLING** OxyContin Tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act. OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product."

Source: FDA-approved label for Purdue's OxyContin.

Appendix III: Databases Used to Monitor Abuse and Diversion of OxyContin and Its Active Ingredient Oxycodone

DEA uses several databases to monitor abuse and diversion of controlled substances, including OxyContin and its active ingredient oxycodone. Specifically, the agency monitors three major databases—the Drug Abuse Warning Network (DAWN), the National Forensic Laboratory Information System (NFLIS), and the System to Retrieve Information from Drug Evidence (STRIDE).[1] DEA also monitors other data sources to identify trends in OxyContin abuse and diversion, such as the Substance Abuse and Mental Health Services Administration's (SAMHSA) National Survey on Drug Use and Health, formerly the National Household Survey on Drug Abuse, and the Monitoring the Future Study funded by the National Institute on Drug Abuse.[2]

DAWN Data

SAMHSA operates the DAWN system, which estimates national drug-related emergency department visits and provides death counts involving abused drugs. DAWN collects data semiannually on drug abuse from hospital emergency department admission and medical examiner data from 21 metropolitan areas and a limited number of metropolitan medical examiners who agree to voluntarily report medical record samples. The emergency department and medical examiner data generally do not differentiate oxycodone from OxyContin, unless the individual provides the information to the hospital or identifiable tablets are found with the person. Although samples from hospitals outside the 21 metropolitan areas are also available, DAWN is not able to make drug-related emergency department visit or death estimates for rural or suburban areas.

NFLIS Data

NFLIS, a DEA-sponsored project initiated in 1997, collects the results of state and local forensic laboratories' analyses of drugs seized as evidence by law enforcement agencies. NFLIS is used to track drug abuse and trafficking involving both controlled and noncontrolled substances and reports results by a drug's substance, such as oxycodone, and not by its brand name. DEA stated that because new laboratories are being added,

[1]Other databases used by DEA to assess changes in drug abuse and diversion include the Drug Early Warning System, the Drug and Alcohol Services Information System, the Treatment Episode Data Set, the National Survey of Substance Abuse Treatment Services, the Uniform Facility Data Set, the Poison Control Center Data or Toxic Exposure Surveillance System, the Automation of Reports and Consolidated Ordering System, the DEA Theft System, and the DEA Field Reports and Investigative Teletypes.

[2]The National Institute on Drug Abuse is part of the National Institutes of Health within the Department of Health and Human Services.

its data should not yet be used for trending purposes. As of March 2003, 35 state laboratories and 52 local or municipal laboratories participated in the project.

STRIDE Data

STRIDE, another DEA database, reports the results of chemical evidence analysis done by DEA laboratories in drug diversion and trafficking cases. Oxycodone data are reported by combining single and combination oxycodone drugs and do not provide specific enough information to distinguish OxyContin cases and exhibits. The database's lag time, which varies by laboratory, depends on how quickly the findings are entered after the seizure of the drug substance and its analysis.

National Survey on Drug Use and Health Data

The National Survey on Drug Use and Health, another SAMHSA database, is used to develop national and state estimates of trends in drug consumption.[3] Prior to 2001, the self-reported survey asked participants if they had illicitly used any drug containing oxycodone. In 2001, the survey included a separate section for pain relievers, and asked participants if they had used OxyContin, identifying it by its brand name, that had not been prescribed for them. State samples from the survey are combined to make national- and state-level estimates of drug use, and because the estimated numbers derived for OxyContin are so small, it is not possible to project illicit OxyContin use on a regional, state, or county basis.

Monitoring the Future Survey Data

The Monitoring the Future Survey, funded by the National Institute on Drug Abuse and conducted by the University of Michigan, annually monitors the illicit use of drugs by adolescent students in the 8th, 10th, and 12th grades. The 2002 survey included new questions using the brand names of four drugs, including OxyContin, in its survey on the annual and 30-day prevalence of drug use.

[3]Self-reporting individuals are interviewed regarding their illicit drug use over three periods—within the last 30 days, during the past year, and during their lifetime. The survey data are limited, as it is not possible to determine specifically which year respondents may have used a drug illicitly, because they are asked both whether they have ever used the drug illicitly in their lifetime and whether they have used it during the past year.

Appendix IV: Comments from the Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

November 6, 2003

Marcia Crosse
Director, Health Care-Public Health
and Military Health Care Issues
United States General Accounting Office
441 G Street, NW
Washington, DC 20548

Dear Ms. Crosse:

Please find the enclosed comments from the Food and Drug Administration on the GAO draft report entitled, PRESCRIPTION DRUGS: Factors That May Have Contributed to OxyContin Abuse and Diversion and Efforts to Address the Problem, (GAO-04-110). The Agency provided technical comments directly to your staff.

We appreciate the opportunity to review and comment on this draft report before its publication as well as the opportunity to work with your staff in developing this report.

Sincerely,

Mark B. McClellan, M.D., Ph.D.
Commissioner of Food and Drugs

Enclosure

General Comments by the Department of Health and Human Service's Food and Drug Administration (FDA) on General Accounting Office's (GAO) Draft Report, *PRESCRIPTION DRUGS: Factors That May Have Contributed to OyxContin Abuse and Diversion Efforts to Address the Problem (GAO-04-110)*

FDA appreciates the opportunity to comment on GAO's draft report which focuses additional attention on the abuse and diversion of prescription drugs.

We have a few general comments regarding the overall report, as follows:

FDA's Regulation of Prescription Drugs

As currently written, GAO's draft report suggests that FDA decided as a matter of policy not to distinguish between types of drugs in regulating promotion. FDA believes it is important to clarify that the FD&C Act makes no distinction between controlled substances and other prescription drugs in its provisions regulating promotion, but that as a matter of general policy, the Agency more closely scrutinizes promotion of drugs with more serious risk profiles.

OxyContin Advertisements Violated the FD&C Act

FDA believes it is important to clarify the content of the warning letter issued to Purdue Pharma. In January 2003, FDA issued a warning letter to Purdue regarding two journal advertisements for OxyContin that minimized its risks and overstated its efficacy, by failing to present any information from the boxed warning on the potentially fatal risks associated with OxyContin and its abuse liability, along with omitting important information about the limitations on the indicated use of OxyContin. The FDA requested that Purdue cease disseminating these advertisements and any similar violative materials and provide a plan of corrective action.

We recommend that GAO include additional information describing the widespread dissemination of the corrective advertisement and the nature of its content, because we believe it gives important information on the extent to which complete and accurate information on OxyContin's risks and its limited indication was disseminated to healthcare providers this year resulting from the warning letter. This corrective advertisement ran for three months and appeared in approximately 30 medical journals. The three-paged advertisement, entitled "Important Correction of Drug Information," contained a two-paged spread, with a "Dear Healthcare Practitioner" letter on one side, which called attention to the warning letter and the cited violations, and directed the reader to the boxed warning and indication information for OxyContin prominently featured on the opposite side of the spread.

Reports of Abuse and Diversion Led to Label Changes and Other Actions by FDA

FDA recommends noting in the report that an important part of the risk management plan in connection with the 2001 labeling changes was that all OxyContin promotional materials be revised to reflect the labeling changes and all future promotional materials prominently disclose this information. As part of the risk management plan in connection with the labeling changes, Purdue was asked to revise all of its promotional materials for OxyContin to reflect the labeling changes. The FDA sent a letter to Purdue, dated August 3, 2001, stating that all future promotional materials for OxyContin should prominently disclose the information contained in the boxed warning, the new warnings that address misuse, abuse, diversion, and addiction, and the new precautions and revised indication for OxyContin. Purdue agreed to comply with this request in a letter dated August 7, 2001.

We also believe it is important to clarify that all three of the patient videos discussed in the report were submitted prior to the labeling change and discontinued as a result of the labeling change and these communications. As the discussion of these patient videos is currently written in the report, it could be misinterpreted that two of the patient videos were submitted after the labeling change as part of Purdue's modification of its promotional materials.

Recommendation for Executive Action

> "To improve efforts to prevent or identify the abuse and diversion of schedule II controlled substances, the Commissioner of Food and drugs should ensure that FDA's risk management plan guidance encourages pharmaceutical manufacturers that submit new drug applications for these substances to include plans that contain a strategy for monitoring the use of these drugs and identifying potential abuse and diversion problems."

FDA agrees with GAO's recommendation and is currently working on the guidance.

Appendix V: Comments from the Drug Enforcement Administration

U. S. Department of Justice
Drug Enforcement Administration

www.dea.gov

NOV 0 5 2003

Ms. Marcia Crosse, Director
Health Care-Public Health and
Military Health Care Issues
General Accounting Office
441 G Street, N.W.
Washington, D.C. 20548

Dear Ms. Crosse:

The Drug Enforcement Administration (DEA) submits the following comments on the facts and findings of the draft report, PRESCRIPTION DRUGS: ***Factors that May Have Contributed to OxyContin Abuse and Diversion and Efforts to Address the Problem (GAO-04-110).***

In general, the report is not as forthright as warranted on the causes/factors relating to the diversion of OxyContin. The root of the problem that this GAO report addresses appears to be the unfortunate convergence of Purdue's marketing techniques and the public/policy focus on pain undertreatment. The DEA has previously stated that the company's aggressive methods, calculated fueling of demand and the grasp for major market share very much exacerbated OxyContin's widespread abuse and diversion. While Purdue highlights its funding of pain-related educational programs and websites and its partnership with various organizations, the fact remains that Purdue's efforts—which may be viewed as self-serving public relations damage control—would not have been necessary had Purdue not initially marketed its product aggressively and excessively. Contributing to the abuse and diversion problem (and the product's excessive availability) is the fact that in promoting this drug to practitioners, Purdue deliberately minimized the abuse risk associated with OxyContin, as the report states on pages 21 and 35. The claim in Purdue's 'educational' video for physicians that opioid analgesics cause addiction in less than one percent of patients is not only unsubstantiated but also dangerous because it misleads prescribers.

In a further example of Purdue's pattern of aggressive pursuit of market share, the report states on page 31: "As part of its marketing campaign, Purdue distributed the usual types of branded promotional items to health care practitioners. Among these items were OxyContin fishing hats, stuffed plush animal toys, coffee mugs, compact discs..." In fact, the use of such branded promotional items for a Schedule II opioid is unprecedented. Distribution of promotional items such as hats, plush toys and coffee mugs is an indicator of Purdue's aggressive, excessive, and inappropriate marketing of their product, OxyContin. The DEA suggests the Department of Health and Human Services restrict promotional materials for Schedule II substances to items related to the practice of medicine or pharmacy.

Increased availability of controlled substances leads to increased opportunities for diversion. Therefore, it is essential that stringent risk management plans are put in place prior to the introduction of these products into the marketplace.

Unfortunately, there are limitations to DEA's ability to document the extent of diversion of specific products and DEA agrees with GAO's observation, on the bottom of page 36 of the draft report, that "data on abuse and diversion are not reliable, comprehensive, or timely." DEA also advocates the development of a system to provide "credible, legally defensible evidence concerning drug abuse trends in America," as stated on page 42 of the draft report. DEA included an additional $750,000 in its 2003 budget request for an enhanced scientific data collection system that would include a National Medical Examiner Information System; however, this request has not been funded. This agency welcomes a recommendation by GAO that more reliable, comprehensive and timely databases be developed.

In addition, there are minor inaccuracies in this report, detailed below:

- First remark, ref page 3, 2nd full sentence of GAO draft report: DEA suggests the following edit to the draft report language (new/replacement language is in bold italics): "Unlike nonopioid pain relievers, ~~OxyContin~~ ***oxycodone, the active ingredient in OxyContin, has no known analgesic*** ~~has no~~ ceiling effect, that is, the dose amount a patient can take can be increased by the physician as needed to relieve pain. ***However, as the dose escalates, there is always a danger of serious side effects, including respiratory depression and death."***

- Page 5, line 9: refers to "…three other opioid drugs, Avinza, Kadian, and Oramorph SR, that like OxyContin are classified as schedule II controlled substances." These drugs should be further identified as ***high dose extended release opioid drugs***, not simply "opioid drugs," here and throughout this document.

- Page 18, first paragraph: states "…a prescription for a schedule II drug may not be refilled, and the patient must see the practitioner again in order to obtain more drugs." While it is correct that schedule II drug prescriptions may not be refilled, a patient is not required to see the practitioner again but must obtain a new prescription.

Please correct the document language noted above to ensure the report's accuracy. The DEA appreciates the opportunity to provide comment to the GAO in these important matters.

Sincerely,

Rogelio Guevara
Chief Inspector

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