DEPARTMENT OF HEALTH & HUMAN SERVICES

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FOR THE HEARING ON

OXYCONTIN: BALANCING RISKS AND BENEFITS

BEFORE THE

U.S. SENATE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

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INTRODUCTION

Mr. Chairman and Members of the Committee, I am John K. Jenkins, M.D., Director, Office of New Drugs, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA or the Agency). I appreciate the opportunity to talk about the drug OxyContin and the steps that FDA has taken in an effort to decrease abuse and misuse of this product while assuring that this drug is used properly and remains available for patients who suffer daily from chronic moderate to severe pain.

Let me assure you that the Agency has taken reports of abuse and misuse of OxyContin very seriously and we have implemented aggressive steps in response to these reports. FDA has worked closely with the manufacturer of OxyContin, Purdue Pharma L.P., to strengthen the warnings and precautions sections of the approved labeling for OxyContin in order to educate physicians, other healthcare professionals, and patients regarding the serious, and potentially fatal, risks of abuse and misuse of this product. FDA has also worked with Purdue Pharma to modify the approved labeling for OxyContin to emphasize that it is approved for the treatment of moderate to severe pain in patients who require around-the-clock narcotics for an extended period of time. FDA also has worked closely with the Drug Enforcement Administration (DEA) to address their concerns regarding abuse, misuse, and illegal diversion of OxyContin.

In order to help you to better understand FDA's actions, I would like to give you a brief overview of the process FDA followed in approving OxyContin and FDA's activities related to regulation of the promotion and marketing of OxyContin.

BACKGROUND

OxyContin is a narcotic drug that was approved by FDA for the treatment of moderate to severe pain on December 12, 1995. OxyContin contains oxycodone HCl, an opioid agonist with an addiction potential similar to that of morphine. Opioid agonists are substances that act by attaching to specific proteins called opioid receptors, which are found in the brain, spinal cord, and gastrointestinal tract. When these drugs attach to certain opioid receptors in the brain and spinal cord they can effectively block the transmission of pain messages to the brain. OxyContin is formulated to release oxycodone HCl in a slow and steady manner following oral ingestion. OxyContin is the only currently marketed FDA approved controlled-release formulation of oxycodone. The drug substance oxycodone, however, has been marketed in the U.S. for many decades and is available in a wide variety of immediate release and combination dosage forms.

Oxycodone, like morphine and other opioid agonists, has a high potential for abuse. OxyContin was specifically developed as a controlled release formulation by Purdue Pharma to allow for up to 12 hours of relief from moderate to severe pain. This dosage form allows patients with chronic moderate to severe pain to have their pain controlled for long periods of time without the need for another dose of medication and significantly reduces the number of tablets the patient must take each day.

When used properly, the OxyContin tablet must be taken whole and only by mouth. If the tablet is crushed, the controlled-release mechanism is defeated and the oxycodone contained in the

tablet is all released at once. If the contents of an OxyContin tablet are injected intravenously or snorted into the nostrils a potentially lethal dose of oxycodone is released immediately. The risk of death due to abuse of OxyContin in this manner is particularly high in individuals who are not tolerant to opioids.

Oxycodone, the active ingredient in OxyContin, is a controlled substance in Schedule II of the Controlled Substances Act (CSA), 21 U.S.C. §801 et seq. which is administered by the DEA. Schedule II provides the maximum amount of control possible under the CSA for approved drug products. Schedule I drugs are considered to have no recognized medical purpose and are illegal in the U.S. outside of FDA approved research.

FDA DRUG APPROVAL PROCESS

Before any drug is approved for marketing in the U.S., FDA must decide--as quickly as a thorough evaluation allows--whether the studies submitted by the drug's sponsor (usually the manufacturer) have adequately demonstrated that the drug is safe and effective under the conditions of use in the drug's labeling. It is important to realize; however, that no drug is absolutely safe. There is always some risk of adverse reactions with drugs. FDA's approval decisions, therefore, always involve an assessment of the benefits and the risks for a particular product. When the benefits of a drug are thought to outweigh the risks, and if the labeling instructions allow for safe and effective use, FDA considers a drug safe for approval and marketing.

OxyContin was reviewed by FDA and was approved for treatment of moderate to severe pain based on two clinical trials that demonstrated that it was safe and effective for this use. Prior to approval, FDA evaluated the benefits and risks of use of OxyContin for treatment of moderate to severe pain and determined that the drug was appropriate for use in this population when used according to the approved labeling.

During the approval process of OxyContin, as with all drugs that are active in the brain, FDA assessed its potential for abuse and misuse. Abuse liability assessments are based on a composite profile of the drug's chemistry, pharmacology, clinical manifestations, similarity to other drugs in a class, and the potential for public health risks following introduction of the drug to the general population. At the time of approval, the abuse potential for OxyContin was considered by FDA to be no greater than for other Schedule II opioid analgesics that were already marketed in the U.S. Based on the information available to FDA at the time of its approval, including the record of other modified release Schedule II opioids, the widespread abuse and misuse of OxyContin that has been reported over the past few years was not predicted. In fact, at the time of its approval, FDA believed that the controlled-release characteristics of the OxyContin formulation would result in less abuse potential since, when taken properly, the drug would be absorbed slowly and there would not be an immediate "rush" or high that would promote abuse. In part, FDA based its judgment of the abuse potential for OxyContin on the prior marketing history of MS-Contin, a controlled-release formulation of morphine that had been marketed in the U.S. by Purdue Pharma without significant reports of abuse and misuse for

many years. At the time of OxyContin's approval, FDA was aware that crushing the controlled-release tablet followed by intravenous injection of the tablet's contents could result in a lethal overdose. A warning against such practice was included in the approved labeling. FDA did not anticipate, however, nor did anyone suggest, that crushing the controlled-release capsule followed by intravenous injection or snorting would become widespread and lead to a high level of abuse.

FDA ACTIONS

Labeling changes

In July 2001, Purdue Pharma, working in cooperation with FDA, significantly strengthened the warnings and precautions sections in the labeling for OxyContin. The labeling for OxyContin now includes a "black box" warning, the strongest warning for an FDA approved product, which warns patients and physicians of the potentially lethal consequences of crushing the controlled-release tablets and injecting or snorting the contents. The indication for use was clarified to reflect that it is approved for the treatment of moderate to severe pain in patients who require around the clock narcotics for an extended period of time.

To help in the effort to curb abuse and misuse of OxyContin, FDA has worked with Purdue Pharma to implement other specific changes in the OxyContin labeling. The new labeling is intended to highlight to physicians, other health care professionals, and patients that OxyContin should be used for the treatment of moderate to severe pain in patients who require around the

clock narcotics for an extended period of time. As part of the labeling changes, a patient instruction sheet was added, which contains information to assist patients in the proper use of OxyContin. These labeling changes are an effort to educate pharmacists, other health professionals, and the general public regarding just how important it is to use this drug properly. The new warnings are intended to lessen the chance that OxyContin will be prescribed inappropriately for pain of lesser severity than the approved use or for other disorders or conditions inappropriate for a Schedule II narcotic.

FDA has developed a patient-information page on its website (www.fda.gov/cder/drug/infopage/oxycontin/default.htm). This site provides important information to patients regarding how to safely use OxyContin, urges patients to keep their supply of OxyContin in a secure location, and instructs patients to destroy unneeded tablets.

As part of a longer-term strategy to address the current reports of abuse and misuse of OxyContin, Purdue Pharma has informed FDA that the company is working to reformulate OxyContin. The reformulation would add an opioid antagonist that would counteract the effects of oxycodone, the active ingredient in OxyContin, if the OxyContin tablet were crushed into a powder and injected or snorted. FDA is working actively with Purdue Pharma to evaluate the safety and effectiveness of such a reformulated product. It must be noted that such a reformulation is not a simple task and it could be several years before any new combination product is developed, tested in clinical trials, and approved by FDA. It also must be noted that the addition of the opioid antagonist to OxyContin to deter abuse means that legitimate patients

would be exposed to a drug substance that they do not need. This could result in adverse reactions in such legitimate patients. These potential safety issues, and assurance that the combination tablet retains its effectiveness in treating moderate to severe pain, must be a part of FDA's review of a reformulated OxyContin product.

Letters to health care professionals

There have been numerous reports of OxyContin diversion and abuse in several states. Some of these reported cases have been associated with serious consequences including death. In an effort to educate health care providers about these risks, Purdue Pharma has issued a warning in the form of a "Dear Healthcare Professional" letter. The "Dear Healthcare Professional" letter was distributed widely to physicians, pharmacists, and other health professionals. The letter explains the changes to the labeling, including proper prescribing information and highlights the problems associated with the abuse and diversion of OxyContin.

FDA approved indication for OxyContin is for the treatment of patients with moderate to severe pain who require around-the-clock opioids for an extended time. An important factor that must be considered in prescribing OxyContin is the severity of the pain that is being treated, not simply the disease causing the painful symptoms.

FDA continues to recommend that appropriate pain control be provided to patients who are living with moderate to severe pain. Although abuse, misuse, and diversion are potential problems for all opioids, including OxyContin, they are a very important part of the medical

armamentarium for the management of pain when used appropriately under the careful supervision of a physician.

Meeting with other government agencies and industry

FDA has met with DEA, the Substance Abuse and Mental Health Services Administration, the National Institute on Drug Abuse, the Office of National Drug Control Policy, the Centers for Disease Control and Prevention and Purdue Pharma, and continue to work collaboratively sharing information and insights needed to address the problem of OxyContin abuse and diversion.

Millions of Americans suffer from some form of chronic pain. The pain can be debilitating and often prevents those afflicted from working or even leaving their home. Many medications, including opioids, play an important role in the treatment of chronic pain. Opioids, however, often have their use limited by concerns regarding misuse, addiction, and possible diversion for non-medical uses. The use of opioid therapy in some patients has shown extraordinary promise, enabling some to return to work and to lead a normal life again. FDA is committed to continuing to work with other government agencies and sponsors to insure that options are available to patients with chronic moderate to severe pain, so that in consultation with their personal physician they can achieve as normal a life as possible.

Advisory Committee Meetings

An FDA advisory committee, a group of non-Agency experts, held a meeting on January 30-31, 2002, to discuss the medical use of opioid analgesics, appropriate drug development plans to support approval of opioid analgesics, and strategies to communicate and manage the risks associated with opioid analgesics, particularly the risks of abuse of these drugs. Committee members agreed that opioids are essential for relieving pain and that a great deal of progress has been made within the last few years to remove the stigma associated with opioid treatment. Members suggested that a balanced approach should be taken to relieve pain for patients and to prevent diversion. They noted that imposing restrictions on use of opioids could have substantial likelihood of hurting legitimate patients and reversing the tremendous progress that has been achieved in the appropriate treatment of pain.

FDA will continue to monitor reports of abuse, misuse, and diversion of OxyContin and other opioids and will work with other Federal agencies and drug manufacturers to help ensure that these important drugs remain available to appropriate patients.

DRUG ADVERTISING

FDA has regulated the advertising of prescription drugs since 1962, under the Food, Drug, and Cosmetic (FD&C) Act and its implementing regulations. The Division of Drug Marketing, Advertising, and Communications (DDMAC), in CDER, is responsible for regulating prescription drug advertising and promotion. DDMAC's mission is to protect the public health by insuring that prescription drug information is truthful, balanced, and accurately

communicated. This is accomplished through a comprehensive surveillance, enforcement, and education program, and by fostering optimal communication of labeling and promotional information to both health care professionals and consumers.

FDA regulates prescription drug advertisements and other promotional materials (called "promotional labeling") disseminated by or on behalf of the advertised product's manufacturer, packer or distributor to health care professionals and consumers.

Title 21 of the Code of Federal Regulations (21 CFR §314.81(b)(3)(i)) requires that advertisements and promotional labeling be submitted to FDA at the time of initial dissemination (labeling) and initial publication (advertisements); a post-marketing submission requirement. The FD&C Act generally prohibits FDA from requiring that advertisements be approved prior to their use (see §502(n)). In other words, FDA's review of promotional materials is generally intended to occur *post hoc* - once the materials have already appeared in public. Accordingly, any FDA enforcement action that FDA takes is *post hoc* as well. Most of FDA's enforcement actions request that sponsors stop using the violative materials. In some cases, FDA also asks sponsors to run corrective advertisements or issue corrective letters to remedy inaccurate product impressions created by false or misleading materials.

FDA is not aware of any direct-to-consumer advertising for OxyContin. There is nothing in the FD&C Act to prohibit such advertising. The advertising and marketing for OxyContin has been directed only to health care professionals. It should be noted that the current approved product

labeling for OxyContin contains a "black box" warning. Boxed warnings are used in labeling to convey serious risks associated with the use of the drug product. The promotional materials of drug products with boxed warnings must present these serious risks in a prominent manner. DDMAC sent a letter to Purdue Pharma dated May 11, 2000, regarding a journal advertisement that appeared in the *New England Journal of Medicine* that promoted OxyContin in a manner that was false or misleading. Specifically, the advertisement implied OxyContin had been studied in all types of arthritis and can be used as first-line therapy for the treatment of osteoarthritis, failed to include important limitations to claims presented from an osteoarthritis study; and promoted OxyContin in a selected class of patients without presenting risk information especially applicable to that selected class of patients. Purdue Pharma agreed to cease dissemination of this advertisement and this matter was resolved with the cooperation of the sponsor.

CONCLUSION

The Agency recognizes OxyContin as a valuable product when used properly. We need to do all we can to ensure that the prescriptions get to the appropriate patients and that labeling and promotion are appropriate for the product. FDA is working closely with the manufacturer to take appropriate action to curb the misuse and abuse of OxyContin. In addition, FDA is involved in the strong interagency effort to address this issue and we are aware we cannot solve this problem by ourselves.

We share the Committee's interest and concerns regarding this drug and would be happy to answer any questions.