FDA Regulatory Processes and Standards for Review and Approval of Opioid Analgesics: An Educational Primer

Office of Special Health Issues (OSHI)
Center for Drug Evaluation and Research (CDER)

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1:00–5:45 p.m.

Hilton (Plaza Ballroom I and II)
1750 Rockville Pike
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Introduction

Terry Toigo, R.Ph., M.B.A., Director
FDA's Office of Special Health Issues, Office of the Commissioner

Terry Toigo, Director of Special Health Issues at the Food and Drug Administration (FDA), opened the meeting by welcoming the panel and participants, and introducing the Agency's Office of Special Health Issues. Created in the 1980s, the Office has worked with patient advocates from many areas, and has been working with public health organizations since 2006.

Opioids have major benefits but also serious risks. This meeting was convened to discuss FDA regulatory processes and standards for review and approval of opioid analgesics as well as to explain FDA's limitations in authority for regulating opioid drug products. The Agency intended the meeting to be a fair and open forum for discussion, one in which FDA would have the opportunity to hear perspectives on abuse prevention and pain management from various constituencies and other government agency staff. The aim was to learn how organizations and FDA can better engage to serve the patient.

Rates of opioid abuse and overdose continue to rise despite risk management efforts and warnings. While FDA has sought to achieve a balance between access and risk mitigation, the agency has received questions about regulation of opioid analgesics, its limitations, and the roles of sister agencies. It is considering how best to balance the requirements of these diverse groups. The Agency believes that *all* stakeholders have a contribution that will have value in this process, and that health professionals and patient advocates are better able to contribute to the evolution of public policy when they understand the issues involved in regulation.

FDA Regulatory Processes and Standards for Review and Approval of Opioid Analgesics

Bob A. Rappaport, M.D., Director
Division of Analgesics, Anesthetics, and Rheumatology Products
FDA's Center for Drug Evaluation and Research (CDER)

Dr. Bob Rappaport, Director of FDA's Division of Analgesics, Anesthetics, and Rheumatology Products, presented an overview of the nature of the opioid analgesic problem, the role of government agencies in tackling it, and the authorities and processes by which FDA approves drugs and monitors drug safety.

For about a decade, the Agency has tried to strike a balance in dealing with various issues related to opioids, but many efforts to overcome these challenges have yet to meet with success. Opiates and the problems associated with their use go back to ancient times. The history of the opium trade can be traced from its primary source on the Indian subcontinent and South East Asia to its expansion West. By the late 19th century opium could be purchased from just about any market on the West Coast of the United States.

As Federal agencies, the Drug Enforcement Administration (DEA), the Centers for Disease Control (CDC), the Food and Drug Administration (FDA), the National Institute on Drug Abuse (NIDA), and the Substance Abuse and Mental Health Services Administration (SAMHSA) share responsibility for managing the risk of controlled drug substances. For its part, FDA's role is to promptly and efficiently review research and to help ensure that drugs are safe and effective. The Agency must abide by laws as it goes about its work. The Prescription Drug User Fee Act (PDUFA II) and the FDA Amendments Act (FDAAA) of September 2007 have made it possible for some funding to be dedicated to postmarket safety.

Dr. Rappaport explained FDA's drug approval process, including Investigational New Drug Applications (INDs), New Drug Applications (NDAs), and Biologics Licensing Applications (BLAs), specifying that most opioid product applications are submitted as 505(b)(2) applications. While none has been approved to date, a number of abuse-deterrent opioid products are in the pipeline, such as those that are tamper-resistant or have noxious substances or euphoria-reducing antagonists added to them to prevent abuse.

The Agency encourages such product development but warns that these products must show a high level of quality; place only factual information in their labeling; and back any claims of decreasing abuse with long-term, community-based epidemiological studies showing that the product's introduction resulted in a decline in abuse.

FDA has worked with sponsors over the last decade to put risk management programs into action for various opioid products, but studies show that they have been unsuccessful in managing the risks of misuse, abuse, addiction and overdose. Fortunately, under FDAAA, FDA has been granted new authorities to implement Risk Evaluation and Mitigation Strategies (REMS) for a number of these products.

Clearly, opioid products are at the center of a major crisis that has resulted in abuse, misuse, and death. A balance needs to be achieved between adequate pain control and managing the risks of these powerful drugs. The process of finding this balance

will require the engagement of all stakeholders, including pain patients, patient advocates and the pain-treating medical community.

Dr. Rappaport observed that this meeting represented the first step in working together with stakeholders to achieve our goals. Everyone must have a part in this process of realizing our common objectives of reducing abuse, misuse, addiction, overdose and death as well as maintaining access for patients with pain.

On February 9, 2009, FDA announced its plans to exercise its authority under FDAAA to require REMS for many of the opioid drug products. The Agency will be meeting with drug companies that manufacture and distribute these products in March 2009 to discuss the design of these REMS, with the goal of devising a single REMS for all opioid drug products. As part of this process, FDA plans to meet with participants in this forum as well as other stakeholders over the next few months. The design and implementation of REMS for opioid drug products will be discussed in an FDA-sponsored public meeting in late spring or early summer.

FDA's Role in Review and Assessment of Potential for Opioid Abuse

Michael Klein, Ph.D., Director
Controlled Substances Staff (CSS)
FDA's Center for Drug Evaluation and Research

Dr. Michael Klein, Director of FDA's Controlled Substances Staff (CSS), explained how the evaluation of new drugs for their abuse potential is based on a comprehensive, interdisciplinary scientific review that involves cross-Agency groups such as the Division of Neurology Products and Division of Psychiatry Products within the Office of New Drug Evaluation as well as the Office of Surveillance and Epidemiology and Center for Veterinary Medicine.

CSS comprises scientists, physicians and pharmacists who recommend risk management practices based on new drug application (NDA) review in areas ranging from pharmacology to clinical effects and safety concerns about abuse and misuse. As part of safety review, the Office advises sponsors on assessing abuse potential, responds to citizens petitions, and collaborates with other government agencies like the Substance Abuse and Mental Health Services Administration (SAMHSA), the National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), and the Centers for Disease Control (CDC).

Dr. Klein took the meeting through the crucial stages of the drug development process, from preclinical through to phase 4, during which time data on a drug's abuse potential can be obtained. If a drug has the potential for abuse, appropriate related information must be included in the formal application for approval of a new drug (NDA). Dr. Klein detailed regulatory tools to prevent abuse, specifically the five levels of drug control, known as scheduling, and risk management programs.

Risk Management Strategies for Opioids and Methods of Surveillance

Gerald Dal Pan, M.D., M.H.S., Director
Office of Surveillance and Epidemiology
FDA's Center for Drug Evaluation and Research

Once medicines go on the market, what are some of the tools and methods FDA has to address drug safety? Dr. Gerald Dal Pan, Director of the CDER's Office of

Surveillance and Epidemiology, examined the various facets of the postmarket safety system. What is the purpose of a postmarket safety system? What are the sources of information on drugs once they're on the market? What are some of the challenges for drugs with abuse potential?

A postmarketing safety system is used to identify new information on drug safety, and to take appropriate regulatory action based on that information. Certain information, such as negative side effects resulting from drug–drug interactions or the use of a drug by a broader population, can only be gleaned once a drug is on the market.

However, within postmarket safety there are definite challenges unique to opioids. In the case of drugs with abuse potential, the standard model applicable to other medicines isn't necessarily the only relevant approach. For instance, FDA might not be looking to identify drug abuse as new adverse effect of the drug, since we know from the pharmacology of the drug that abuse is likely to occur. In addition, the intended patient is often not the person who experiences the harm, since abuse and misuse of opioids often occurs in the setting of drug diversion. In this case, the Agency wants to quantify patterns of abuse and figure out how to lessen them. FDA needs to know how often the drug abuse is happening, but quantifying these events is challenging because reporting practices vary and the Agency doesn't receive most adverse events reports.

It's also hard to tease out certain facts from spontaneous reports. We often don't know the source of the medication, if there has been medication theft, overuse of prescribed drugs or overdose due to a suicide attempt.

Risk management is an iterative process. In the pre-approval of a drug, under Section 505-1, FDA may determine that a Risk Evaluation and Mitigation Strategy (REMS) is needed to ensure that the drug's benefits outweigh its risks. It will then inform the sponsor and require it to submit a REMS. In this instance, the REMS is approved with the original drug application. However, FDA may decide after approval that a REMS is needed if the Agency becomes aware of new safety information that indicates that such a strategy is required to ensure that the drug's benefits outweigh its risks. In this case, the REMS is approved as a supplement to the application.

REMS elements include medication guides and patient package inserts, a communication plan (such as letters to healthcare providers and dissemination of information through professional societies about any of the drug's serious risks), and elements to to assure safe use.

Dr. Dal Pan reviewed some of the elements to help ensure safe use, such as specially certified pharmacies, practitioners or healthcare settings, which dispense drugs with serious risks, among other requirements, as well as the timetable for assessing REMS.

FDA has put into practice new FDAAA authorities. This has involved creating cross-disciplinary teams to ensure that FDAAA provisions are applied consistently; developing standard templates for approval letters and for REMS; and working on guidance for industry to make processes more transparent.

Questions and Answers

Dr. Kirk Van Rooyan of Sacramento, California is a Patient Advocate and father of Patrick Van Rooyan, who died on July 9, 2004 at the age of 24, after ingesting just one OxyContin. He had no other drugs in his system and only a small amount of alcohol.

Dr. Van Rooyan: Prior to implementing REMS, which stem from FDAAA, did FDA have the authority to alter prescription labeling?

FDA (Dr. Dal Pan): In the postapproval setting, the Agency didn't have that authority. Prior to the enactment of FDAAA, certain products had Risk Minimization Action Plans, or RiskMAPs, According to the FDAAA, products that had certain restrictions on use, generally as part of RiskMAPs, were deemed to have a REMS once FDAAA took effect.

Dr. Van Rooyan: Does FDA take into consideration clinical studies?

FDA (Dr. Dal Pan)**:** We look at all the data we have in the post-approval experience. Sometimes at the time of approval we know we'll need REMS, at other times we need REMS in the postmarket phase.

Dr. Art Van Zee is a physician at Stone Mountain Health Systems in the coalmining town of Saint Charles, Virginia, where he has witnessed enormous problems resulting from OxyContin abuse.

Dr. Van Zee: It seems to me that prescription drug abuse is often a result of misprescribing. It appears that there is no requirement for demonstration of competency on the part of the physician. Under FDAAA, would there be regulatory measures to require a physician's competency, specifically regarding methadone?

FDA (Dr. Rappaport)**:** Yes, there are features in REMS like educational programs, which haven't been terribly effective so far. Perhaps there is a need for programs that have a feedback loop that would show physicians knew when to treat and how to treat patients. FDA is working with DEA and other agencies on this. It is something on which we agree with you; it could be an effective part of REMS. We're looking for this kind of information from stakeholders.

Steve Hayes, is an attorney and Director of Novus Medical Detox Center of Pasco County, Florida.

Mr. Hayes: There's a lot of information about under treatment of pain but I've seen the opposite. Is this going to be a transparent process so that we can see information that shows there's a lot of pain to be treated?

FDA (Dr. Rappaport)**:** We're going to get as much input from the scientific community and all stakeholders as we can so we can get to the point by the time of the public hearings where we have a sense of the right ways to move forward in developing REMs.

Dr. Joel Saper is past president of the American Headache Society, which was founded to treat intractable headaches.

Dr. Saper: There is compelling scientific data supporting the adverse effects of opioids in treating chronic headache. The first point I'd like to make is: take everyone off of opioids. My second point is that I'd asked that guidelines be developed for prescribing opioids. I resigned from the committee because there was intense resistance to the effort to include language that requires criteria for initiating opioids, guidelines for initiation. There is a negative attitude about this notion and compelling data to suggest other ways of treatment. Many of us doctors are willing to help you.

FDA (Dr. Rappaport)**:** I am aware, as a neurologist, of how opioids are used inappropriately for chronic headache disorders. This is exactly the type of misuse we are trying to combat with a REMS..

Joanne Peterson is a Patient Advocate for Prescription Drug Reform in Massachusetts. She is Executive Director of the grass roots organization Learn to Cope (LTC), which gives parents and children an opportunity to learn how to intervene effectively in their children's addiction.

Ms. Peterson: In Massachusetts, the leading cause of injury death is opioid overdose. Given these numbers, will this be taken into consideration now? Does the solution for pain have to be an opiate? Percocet, for example, is wildly out of control. It's not always the family's fault. I hope taking this into consideration will be part of changes we'll see.

FDA: (Dr. Rappaport) We clearly think there are proper and improper uses for opioids. We now have new authorities that allow us to more fully addresss this problem.

Panel Discussion—Roles of the Drug Enforcement Administration (DEA), FDA, and National Association of State Controlled Substances Authorities

Mark Caverly, Chief
Liaison and Policy Section, Office of Diversion
Drug Enforcement Administration (DEA)

Jason Woo, Associate Director for Scientific and Medical Affairs,
FDA's Center for Drug Evaluation and Research (CDER)

Karen Tannert, President
National Association of State Controlled Substances Authorities

This part of the meeting dealt with the relationship between FDA and enforcement authorities; monitoring the criminal justice system; the role of DEA and compliance with laws and regulations, inspections, and investigations; and the states' role from the National Association of State Controlled Substances Authorities.

National Association of State-Controlled Substance Authorities (NASCA) (Karen Tannert): Some 25 years ago state regulatory authorities were struggling with regulations coming down the pipeline. They realized states around them had the

same problem. There had to be some way states could come together to talk about controlled substances.

NASCA is primarily education-oriented. We look at what worked in other states, find some baseline language (www.NASCSA.org). We are the people that control access. States can do something that is more restrictive than DEA, e.g. can put a drug in Schedule III in Schedule II. We are the observer, tracker and limiter. We are particularly cracking down on pill mills.

In terms of our existing relationship with state medical boards, our role is one of education. Individual states might have more interaction with them. To have an impact on the medical profession one has to go through the legislature.

DEA Drug Enforcement Administration (Mark Caverly): One of DEA's roles is scheduling, which it shares with FDA. The Office of Diversion Control is tasked with preventing diversion of legal controlled substances, that is, unintended use of controlled substances.

President Nixon was responsible for establishing the DEA, which replaced a patchwork of laws going back to 1914. The Controlled Substances Act of 1970 (CSA) consolidated over 50 laws regulating the manufacture, distribution, import/export and dispensing of controlled substances and listed chemicals. The intent was to create a closed system of distribution. It is the legal foundation for U.S. law, forming a system of compliance. DEA looks strongly at the issue of over or inappropriately prescribing.

CDER Office of Compliance Role in Drug Safety (Jason Woo): The mission of FDA's Office of Compliance in CDER is to promote and protect public health through strategies and actions that minimize exposure to unsafe, ineffective, and poor-quality drugs. Our authority comes from the Food, Drug and Cosmetics Act.

Our role is one of compliance; we assure the integrity of drug information and products (e.g., is the information or product good, reliable, verifiable and complete?)

Thousands of prescription drugs are marketed without approval. (About 2% of drugs are unapproved and many older drugs haven't gone through the approval process). Some firms specialize in producing these drugs. Our challenge is to balance the public need for these medicines with whether they could produce a hazard to consumers. We must decide whether to remove the drugs or help them come into compliance. We encourage drug producers to submit an application, including information on the manufacturing process.

Hydrocodone is an example of this challenge. While there are seven approved versions of the drug, there are 200 unapproved drugs on market and many health problems associated with it. We are trying to reduce the confusion.

Questions and Answers

Larry Golbom is a Patient Advocate, a registered pharmacist and host of Prescription Addiction Radio, which he founded after his 17-year-old son became addicted to OxyContin.

Mr. Golbom: I have a question for Mr. Caverly. I'm trying to understand DEA a little bit better. Over the past 10 years Florida's population has increased by 14% and opioid use has shot through the roof. Is it time to reduce the quota?

Mr. Caverly: We don't give companies everything they ask for. We increase quotas pursuant to companies that are producing for legitimate needs. We have also cut quotas and perhaps we should be stricter. We do try to keep balance.

Dr. George Kolodner is a practicing addiction psychiatrist, representing the American Psychiatric Association.

Dr. Kolodner: What luck have you had with doctors who over prescribe?

Mr. Caverly: We are monitoring doctors prescribing; 38 states have monitoring programs. We obtain information from doctors, pharmacies complain about doctors, medical boards call us when they have doctors they're disciplining. We have systems that monitor purchases. I wish there were a more effective way of monitoring prescribing of drugs.

Other Government Agency Activities: How National Institute on Drug Abuse (NIDA) Initiatives Promote Understanding of Prescription Opiates

Betty Tai, Ph.D.,
Director
Center for the Clinical Trials Network, NIDA
National Institute on Drug Abuse, NIH

Prescription or over-the-counter drugs account for 7 out of 11 of the most frequently abused drugs among 12th graders. In 2008, 15.4% of this age group reported abusing prescription drugs. In 2007,1.7 million people 12 years of age or older abused or were dependent on pain relievers.

Pain is experienced by 10%–20% of the population, with 50 million people suffering chronic pain. While clinical experience confirms that opioid treatment can help selected patients experience a better quality of life, use health care services less, and be more productive, it carries with it the risk for abuse or addiction. Alternative medications, including methadone and buprenorphine, have been developed, which treat opioid addiction by suppressing withdrawal symptoms and reducing the patient's need for short-acting opioid drugs.

Dr. Tai detailed the different types of outreach programs available to practitioners and researchers in the clinical management of chronic pain, including delineation of clinical practices that minimize the risk of opioid addiction and the development of guidelines for early detection and management of addiction to pain relievers.

Substance Abuse and Mental Health Services Administration (SAMHSA)

Initiatives to Educate Prescribers and Consumers and Treatment Resources

Nick Reuter, Senior Public Health Adviser
Division of Pharmacological Therapeutics
SAMHSA's Center for Substance Abuse Treatment

Prescription drug abuse is a major public health challenge. In 2007 alone, more people started to abuse pain relievers than any other substance. Among young adults that year, non-medical use of prescription pain relievers rose 12% even while use of illicit drugs fell. About 56% of people got a prescribed drug from a friend or relative.

Mr. Reuter reviewed the different kinds of opioids, current statistics on non-medical use of opiates and the Agency's efforts to educate prescribers and consumers. Resources for treating opioid addiction in various states, including methadone and Buprenorphone treatment as well as online training for physicians were also discussed.

Open Discussion, Next Steps and Closing Remarks

Dr. Douglas Throckmorton, M.D., Deputy Director
FDA's Center for Drug Evaluation and Research

Terry Toigo: We are very grateful to have patient representatives with whom we've been speaking over the past year here today. They have spent their own money to come to this meeting and participate.

FDA (Dr. Throckmorton)**:** As we thought about this meeting, one of the most important reasons to convene it was to have a means whereby people could talk to each other who wouldn't ordinarily have that chance. I hope you've had an opportunity to look across the table. The point is to humanize the complexity of this issue. How do you achieve this? Many of us have very strongly held views. Going forward, we hope you're asking each other questions and we encourage that.

Dr. Kirk Van Rooyan: I commend FDA for being involved in this effort. I hope we can continue. Mr. Reuter, your statistics reinforce clinical studies – 56% of prescription drugs came from friends and relatives, 81% from a single physician! Having lost a stepson, I wonder, why isn't there some form of mandatory competency required?

Mr. Larry Golbom: Dr. Rappaport, the way I feel is I'm delighted. I have been angry for five years. This is a new beginning and I'm looking forward to this process. I have a new attitude. You're allowing us to become a part of the solution and I'm very happy about that. I think there should be a moratorium on these drugs, any drugs that contain an opiate. They've been over distributed, over marketed, they've misled pharmacists and the medical profession. They continue to mislead the media. While we're trying to hammer out this solution, can you promise no more approval of opiates until regulations?

FDA (Dr. Throckmorton)**:** This was a question asked yesterday at a press conference. It's important for us as regulators to separate criminal behavior, which should be punished, from our task as regulators, which is to find the best way to make these drugs safely available to the American public. I prefer to leave the criminal behavior to those whose job it is handle that issue and focus my attention on developing ways to mitigate these risks.

Barbara Van Rooyan: (Wife of Dr. Kirk Van Rooyan) I am among the authors of the citizens petition. This is the first day I feel we've been heard. I'm glad we've persevered. My question is a bit of a repeat of Dr. Saper's. We get wrapped up in the debate of under-treated pain. The real question is, how do we best treat that pain? What we have to look at, Dr. Throckmorton, is that all the recent studies have documented the high risk and demonstrated lack of efficacy of these drugs. This is an essential piece of all of that. I'm asking that as you develop these REMS and request for changes in indications that you take these studies into consideration.

FDA (Dr. Throckmorton)**:** I have received those articles, read them, and look forward to sharing them. That is the conversation that we need to have here.

Dr. Van Zee: I would like feedback on the suggestion that indications of high-potency opioids need to be re-examined. The world is a different place from 1995. I think risk–benefit analysis of sustained release opioids is very different now. They have significantly higher risk. There is inadvertent risk of overdose and death, higher risk of opioid addiction, when abused. Recreationally, opioid users, young people, when exposed to high-potency opioids became rapidly addicted. Risk–benefit analysis needs to be looked at. Immediate and sustained release opioids are comparable in efficacy. I'd refer you to that. This could be something that could be part of future programs. Have Dr. Tai look at this issue. Have sustained release opioids changed to treat people with cancer, etc. Have access through a compassionate use program.

FDA (Dr. Rappaport)**:** The reason we haven't changed the indication is that the difference between moderate and severe pain is a totally subjective, individual experience. We've looked at the data; the impact of moderate pain is quite severe because it interferes with activities of daily living. Mild, moderate and severe are colloquial terms that patients and physicians use to communicate with each other. These terms are not the same for every doctor. It's up to the doctor and patient to decide at what point he or she needs the more potent product. Were we to limit it to severe pain, then patients would just say they were in severe pain. These are the reasons we made the decisions we did over the last decade; but we are still open to hearing different points of view on this issue.

Ms. Penney Cowan is Founder of the Americans with Chronic Pain Association.

Ms. Cowan: What I haven't heard here today is improve the quality of life and help them function better. We want to feel better yesterday. I want immediate relief. My concern is education to the consumer. What does REMS mean? Most consumers don't understand it and this really does have an impact on them. Language is important so they can make informed decisions. If it weren't for proper pain medication people couldn't hold their jobs.

FDA (Dr. Throckmorton)**:** Patients have to be active participants in their treatment and for that they have to be well informed. We commissioned a study on consumer medication information (CMI), the information stapled to a prescription that is not written by the manufacturer and not from FDA. The law required FDA to look at that. Of the prescriptions dispensed, 95% would be accompanied by useful prescription information. The study showed this information wasn't useful.

Ms. Cowan: People don't read anymore. We need things like public service announcements. We have to treat pain appropriately.

FDA (Dr. Throckmorton)**:** FDA doesn't rule out the need for other types of media.

DEA (Mr. Caverly)**:** The DEA has been looking at "Take Back" programs. The ultimate users who received controlled substances have a supply of medicine that they don't use. It becomes a source of supply for potential diversion and misuse. It makes sense that you could dispose of these controlled substances in the right fashion. What do you do with these medicines? DEA concluded that currently there is nothing in place that permits the ultimate user to do anything but consume the medication. It's a pretty thorny issue. So in a Notice published in the Federal Register on January 21, 2009, DEA reached out to the public – law enforcement, hospitals, any interested parties – to give us information. We think there are shortcomings in the Controlled Substances Act. There are environmental concerns. We're looking to the public to assist us.

Dr. Kolodner: One of my patients was killed by another physician, who gave him medication. This physician is still practicing in Montgomery County. Have you had doctors groups identify this as a problem? The American Medical Association was represented here earlier. How are they involved in this?

FDA (Dr. Rappaport)**:** The Agency plans on meeting with representatives from various medical societies.
Dr. Kolodner: It's important to involve medical boards and ensure that they participate in these education efforts.

Mr. Stephen Porada is the Director of the American Society of Pain Educators.

Mr. Porada: Will the current pipeline of pain medications be held up in their approvals while we figure out REMS? Will you only accept REMs with a patient registration component attached to it?

FDA (Dr. Throckmorton)**:** We can't comment on any actions we would take. But that's the sort of information we're looking to get.

Mr. Hayes: Maybe you could have something whereby it would be illegal for a prescription medical product to be in someone else's possession? Is that something that could be instituted?

FDA (Dr. Throckmorton)**:** Those pieces of paper probably say something like that. What would the CMI say? If you picked up a prescription at 10 different pharmacies you could get 10 different types of information.

Mr. Steve Hayes: A lot of people don't read that information. What if you get people to sign it?

FDA (Dr. Throckmorton)**:** We're trying to tweak our messages to tailor them to adolescents.

Sandra Kresser is a bereaved parent of Joshua Sam Kresser, who died on September 30, 2006 from a lethal combination of Vicodin, Ativan and Soma that had been prescribed by a doctor who knew of her son's opiate addiction. Sam initially became addicted to opiates when a doctor prescribed OxyContin for his back pain.

Ms. Kresser: Although I am an advocate for prescription drug reform, I am not against opiates prescribed on a compassionate basis. My son Josh became addicted to prescription opiates when a doctor prescribed OxyContin for his two herniated disks. Doctors continued to prescribed opiates for my son, knowing fully of his history of addiction. This is a pervasive problem in all states. Why hasn't FDA developed a more stringent policy with the states?

FDA (Dr. Throckmorton)**:** We are still looking at this enforcement piece and how best to achieve this. State boards have tremendous responsibility. It would be good if there was a suggestion about how we could help them. Education is the most efficient thing a board could engage in. If you have any ideas, we want to hear them.

FDA (Dr. Rappaport)**:** When we have factual information on clinicians acting inappropriately, it provides us with additional support for employing our authority to create appropriate restrictions under a REMS..

Micke Brown is Director of Communications at the American Pain Foundation.

Ms. Brown: We need to understand our common ground. I think it is very important regarding opiate prescriptions that we understand our responsibilities and keep these drugs out of harm's way, keep them from people they aren't intended for. What can we do working with populations using these drugs?

FDA (Dr. Throckmorton)**:** The Partnership of Drug-Free America is one organization that deals with appropriate use and appropriate disposal.

FDA (Dr. Rappaport)**:** The Agency is sensitive to younger Americans – many young people already have experience with prescription opioids before the 12th grade! NIDA has an aggressive campaign going on directed at schools. It's an educational issue for parents and school to understand risk. The other element is that if, through screening you find someone abusing drugs, then what do you do? Do you find effective treatment that you can refer patient to? Treatment is being very severely stigmatized. The standard is not really up to what we wish for. We need to bring drug addiction into mainstream medical practice. Doctors need to ask, "Do you smoke, drink, use other substances?"

Ms. Brown: We don't have enough pain specialists, enough specialists for co-morbidities. We have to start treating this from a disease model.

FDA (Dr. Throckmorton)**:** Efforts are under way to reduce diversion.

Ms. Brown: We could be really effective if we learned from abuse and diversion.

FDA (Dr. Throckmorton)**:** This relates to the development and utility of electronic medical records. With a database, it's easier to spot if an opioid has already been prescribed. It's a red flag.

Dr. Leonard Paulozzi is Medical Epidemiologist at the Centers for Disease Control (CDC).

Dr. Paulozzi: Regarding REMS, I didn't hear who's responsible for collecting the data.

FDA (Dr. Rappaport)**:** The companies are required to follow this information and collect all appropriate data based on the statute.

Dr. Paulozzi: Who would evaluate the mitigation?

FDA (Dr. Rappaport)**:** It's the companies' responsibility to assess their REMS.

FDA (Dr. Throckmorton)**:** We need to be able to construct metrics, need to be able to evaluate REMS.

Dr. Paulozzi: I'm not encouraged by an education strategy. Will FDA consider restricted distribution?

FDA (Dr. Throckmorton)**:** We're at the beginning of a process. Education may not be the only piece, but part of the solution.

FDA (Dr. Dal Pan)**:** Assessing the impact of risk mitigation strategies is a relatively new area. The law is a year and a half old. Understanding what works is and will be complicated. We need to look at tools to see what works at different levels - the process level, the behavior level, and the health outcome level. Are we achieving the health outcomes we want?

Dr. Paulozzi: I advocate evaluating and moving expeditiously.

FDA (Dr. Throckmorton): Part of the process is getting in people like you. We need specifics on the ways to restrict access.

Gary Franklin is a Research Professor at the University of Washington and a member of the American Academy of Neurology.

Professor Franklin: I think it's dosing run amok. The question is about the standard or criteria FDA uses to approve a new drug. Does it enhance the threshold *a priori* of improvement in pain and function? What is the status of using such criteria?

FDA (Dr. Rappaport)**:** We definitely take into consideration the amount of improvement and ask all sponsors to look at function as well. And ultimately what we're looking at when we get an efficacy outcome, we're still going to do a risk–benefit analysis. We're doing a comprehensive evaluation.

Professor Franklin: The Academy's plea would be to use improvement in pain and function—setting a threshold. Jane Ballantyne left but her article mentioned rampant

tolerance; I only heard one person mention tolerance. How are you approaching this issue?

FDA (Dr. Rappaport)**:** We certainly take into consideration the possibility that the chronic use of opioids results in tolerance. It clearly happens in animal models but the actual degree of tolerance that happens in people is the subject of a considerable clinical debate.

Professor Franklin: In terms of tracking outcomes, you need to get data on these adverse events. We can tell you how many patients have sleep apnea, for example, you should partner with state agencies.

FDA (Dr. Rappaport)**:** That is the purpose of the next set of stakeholder meetings.

Professor Franklin: We're doing a web-based survey on primary care doctors. For example, "Are you comfortable using opioids or very uncomfortable?" So this is something to keep in mind regarding REMS. Doctors are begging for additional tools that they can hand to patients. What is contributing to more and more mortality? We don't know the breakdown. Which sectors? The amounts being prescribed are related to all of that. I strongly encourage you to look at doing a guidance because that's what's missing out there.

FDA (Dr. Throckmorton)**:** Did the guidelines you put in place in Washington State have an impact?

Professor Franklin: The web-based survey, the data coming in, it will have an impact. We need to do a more complete evaluation. The mortality rate has moderated in 2007, but I can't tell you that the guideline had anything to do with that. There is a paper that will be published that will explain this.

Chip Amoe is the Assistant Director of Federal Affairs at the American Society of Anesthesiologists.

Mr. Amoe: I heard nothing about the status of NASPER [National All Schedules Prescription Electronic Reporting, a national prescription monitoring program], using that tool. We worked closely with DEA to craft legislation that was a useful tool for physicians to track and see whether patients were doctor shopping. We wanted to find out where we are with the status of that.

DEA (Mr. Caverly)**:** NASPER has not been funded. Congress enacted it but there are no funds to implement it.

Mr. Amoe: Consumer groups, that might be a way to direct your energy. Another aspect as we move forward is the promise of electronic medical records; there's an opportunity use those.

DEA (Mr. Caverly)**:** There's money for prescription monitoring but Congress focused on initiating state grants.

DEA (Mr. Caverly)**:** There is a perception in society that pharmaceutical drugs are safer than illicit drugs. Since they are manufactured under FDA guidelines they must be safer to abuse than illicit drugs. It's not just a regulatory or enforcement issue.

We look for instantaneous relief. This is a problem at many levels in our society. Dealing with the diversion of prescription drugs is very difficult, particularly if there is slippage within one's own family. We have to teach our kids.

FDA (Dr. Throckmorton)**:** When we find evidence that FDA products are used inappropriately my focus as a regulator is to support appropriate use. In terms of holding people accountable for their behavior—I turn to Jason—I send inappropriate use to people who deal with it.

FDA (Dr. Woo)**:** Lock up your medicines supply.

Ms. Peterson: A man down the street supplied my son with OxyContin. On the subject of accountability—I'd love to have pressed charges, because he's handicapped my son. My son just had a relapse after four years. I also wonder why this man was getting this OxyContin. By the time I went to the police, it was too late. The point I wanted to make is that this could hit any family. Every family deals with some sort of addiction. Alcohol is widely accepted, but prescription drugs are another thing. I read one obituary where a young man was on a methadone program as a choice of treatment. He went to a psychiatrist who gave him the drug Clonapin and he died. Are psychiatrists allowed to talk to a methadone clinic? If they see Clonapin, should they be addressing that?

FDA (Dr. Throckmorton)**:** That is the sort of tragedy that we all want to change.

Marcie Bough is the Director of Federal Regulatory Affairs for American Pharmacists Association.

Ms. Bough: We have many guidances that we've issued about methadone and other opioids. One state has chosen to deal with that through a prescription monitoring program. The two parties need to talk to each other. Despite our best efforts, we have trouble preventing that dangerous interaction. But we can't tackle methadone prescribed for pain; that's the population we don't have direct access to.

Peter VanPelt is Senior Manager, Corporate Alliances for the American Pharmacists Association.

Mr. VanPelt: Marcie, I appreciate the opportunity to provide feedback. It's encouraging to see information from SAMHSA about the risk of opioids, keeping them out of reach and how to properly dispose of them. Making them user friendly is a good example as we look at medication guides. Do you have a good response on that pilot program?

Ms. Bough: There wasn't too much information.

Mr. VanPelt: That's what we keep hearing. Too much information isn't helpful either. We'll be working with FDA at the end of February on how we can fix the system for all that patient information as a tool to interact with patients, that they're understanding the information. It's encouraging that it's the same systems for the 24 targeted opiates. Thank you for opportunity to be here today.

Mr. Peter Jackson is a Patient Advocate. He is the father of Emily Jackson, who died on August 18, 2006 at the age of 18 years, after taking one OxyContin pill offered to her by a relative. It was the only time she had taken the drug.

Mr. Peter Jackson: I represent advocates for prescription drug reform—bereaved parents, doctors, support counselors; we are working together to address this problem. I appreciate Dr. Tai's comments on stigma. We use the word 'stigma' when we talk to each other about the reaction of most people to the problems associated with prescription opiates. What reminds us of this reaction is FDA's response to the peanut butter contamination. It was immediate and impressive. It leaves us feeling, where's the response to the thousands of people who die from prescription opiates? I'd like to remind everyone that a large part of problem we're here to talk about today is teenagers. They make bad decisions. All it takes is one decision like my daughter Emily's. Education is important, proper disposal is important but there's always going to be a risk with teenagers. They think it's a safe way to experiment with drugs. We need to respond to that as a society. I'd like to thank FDA for putting on a productive workshop.

Ed Vanicky is a member of Advocates for Prescription Opioid Drug Reform. His wife Mary Jo died of acute OxyContin intoxication on July 27, 2000. After her death, it was discovered that the license of her prescribing pain management physician was on probation for excessive prescribing of narcotics to habitual drug-users, prescribing for no legitimate medical purpose, fraud, and other charges.

Mr. Vanicky: Back in January 2000, my wife was in a car accident and suffered a herniated disc. She was referred to a pain management physician, who prescribed OxyContin. Over the course of five months, her dosage strengths were increased to 40 milligrams. She died in July 2000. The coroner wanted to know where she got the OxyContin. I started doing research and learned about this pain management physician who lied about running tests on my wife but never did any such thing. No one should have to die from a bad back. Are any of these drugs going to be reclassified?

FDA (Dr. Throckmorton): We have to figure out how to prevent that from happening. Do we have the commitment to find out what the right answers are? We see the devastation. We really do believe that we need to change that. Right now we need to have more information.

Mr. Vanicky: This particular physician's license was on probation. Does FDA have plans to tighten up on things like that?

FDA (Dr. Throckmorton)**:** You're pointing out how complex an issue this is.

Mr. Vanicky: Are there any plans for DEA to recruit more agents?

DEA (Mr. Caverly)**:** There is a perception that there is a DEA investigator behind every bush. But we do have a basic class scheduled. We'll have a class of 40 to 50 new diversion investigators.

Mr. Vanicky: Concerning opioid abuse in the military, how involved is FDA in helping the military?

SAMSHA (Mr. Rueter)**:** SAMHSA has a program for veterans. There are many incidences with veterans in active duty sharing medications and we have program targeted at veterans.

Dr. Van Zee: There are tamper-proof opioid dispensers under development, which dispense the opiate at the time it's supposed to be taken. It's a promising solution that could decrease diversion. It seems that it could decrease to some degree diversion, that as things progress that this dispensing system could be required for all drugs.

FDA (Dr. Throckmorton)**:** There is appropriate use of these products, inappropriate use leading to a crisis of abuse. We don't want the latter to happen and don't think the status is sustainable. I speak for everyone that we do have commitment to make that change and find a way to include the safest use of these products while checking their availability. What gives me hope is that commitment and the energy that I hear here today. We require all of the communities we heard today to make a difference for all of the reasons we heard—we need that collaboration to succeed. We have to look at some solutions we've discarded in the past, turn to education, guide appropriate use, to educate physicians. We have to participate; we also owe it to this moment. We have the opportunity to revisit what we're doing regarding opiates. Please comment, please attend meetings! We do listen. We read these things very carefully. If we don't respond to you individually, it doesn't mean we're not paying attention. I'm grateful for Mark and Nick demonstrating their commitment to try and make a difference in this effort. We have a meeting with DEA on Friday to look at ways in which we can help and facilitate working together in the spirit of collaboration. Nick and I are working on a guideline for methadone. That's collaboration. Without that we're not going to succeed. Send e-mails to me. We take them as seriously as we possibly can.

I would like to thank Terry for setting this meeting up. Thank you to everyone for coming today and sharing your stories of loss. You can work with the companies that got those letters. We look forward to working with you more in the future.