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Quick Pulse

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FDA Advisory Committees Recommend Approval of Purdue's Reformulated OxyContin

Gaithersburg, MD
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The FDA's Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) jointly recommended approval of Purdue's reformulated OxyContin (oxycodone controlled-release) by a vote of 14-4, with one abstention. The FDA had previously turned down the new OxyContin, but panel members agreed that the data were much improved, though they asked for a post-marketing study due to continued concerns about safety. Although the panel expressed concern about the continued misuse and abuse of OxyContin, it saw the reformulated drug as the lesser of two evils.

The four "no" votes included the acting panel chair who said that it was unconscionable that the drug be approved without a Risk Evaluation and Mitigation Strategy (REMS). In February 2009, the FDA said that it would start working on a REMS for opioids, but no plan has been announced yet.

The 19 voting members included 4 anesthesiologists, 4 pharmacists, 2 patient representatives, 2 pediatricians, a biostatistician, an epidemiologist, a pain expert, an internist, a dermatologist, a cognition expert, and a health researcher.

Background

The misuse and abuse of OxyContin is a continuing problem according to the National Survey on Drug Use and Health (NSDUH) and the Drug Abuse Warning Network (DAWN). A review conducted by Purdue showed that the most commonly used route for misuse and abuse of OxyContin is orally, but experienced abusers inject and/or inhale crushed tablets.

The reformulated controlled-release (CR) tablets containing 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg oxycodone are intended for twice daily dosing (Q12H) for treatment of moderate-to-severe chronic pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

The tablets are an eroding matrix formulation of oxycodone in which the release of the drug is controlled by the polyethylene oxide matrix. Purdue claims that the reformulated tablets are bioequivalent to the original OxyContin product. The company proposes to market only the reformulated OxyContin and to remove the current OxyContin from the market. It also said that it would not include any language related to tamper resistance in the labeling.

The panel rejected the new formulation in May 2008 due to concerns that:

- The tools used to assess the new formulation regarding abuse, misuse, and diversion were inadequate.
- The rigor of the scientific data was insufficient.
- More pre-marketing tests were necessary.
- The testing methods needed independent validation.
- More information was needed to address safety concerns related to the injection of the gelatinous matrix that forms when aqueous media is added to the crushed tablet.
- There would be continued misuse of the non-reformulated 60 mg and 80 mg doses, which Purdue wanted to keep on the market with the idea of reformulating them in the future.

THE FDA PERSPECTIVE

The Controlled Substance Staff (CSS) of the FDA's Center for Drug Evaluation and Research (CDER) reviewed the "extensive" company *in vitro* testing submitted to the FDA in March 2009 and concluded that the new formulation's tamper-resistant properties are limited but may be better than currently available OxyContin.

The only background documents were a 2003 Government Accountability Office (GAO) report on OxyContin abuse, a 2006 NSDUH summary, the DAWN substance abuse estimates for 2006, and the CSS memo. The memo said, "Information on routes of administration involved in the non-medical use or abuse of OxyContin tablets is limited. Nevertheless, a review conducted by (Purdue) of the published literature and analysis of the 2006 NSDUH data shows that the oral route is the most commonly used route for the misuse and abuse of OxyContin. However, more experienced abusers report injecting or inhaling crushed tablets. Nevertheless, the percentage of OxyContin abusers who chose to use parenteral routes seems to be low when compared to the number of abusers who use the oral route."

The CSS reviewer concluded:

- Detailed *in vitro* testing to characterize tamper-resistant properties was conducted on all dosage strengths of reformulated OxyContin.
- As a product that is bioequivalent to OxyContin, all oxycodone blood levels produced by the intact reformulated product are expected to be the same as those produced by OxyContin at all points in time after oral administration.
- The proposed reformulation may provide enhanced protection over that of the currently available OxyContin for the intended population against dose dumping when tablets are accidentally crushed or chewed.
- The tamper-resistant properties of the reformulated OxyContin are limited. However, it may provide an advantage over the currently available OxyContin.

OxyContin was approved on December 12, 1995. An 80 mg tablet was approved in 1996, and a 160 mg tablet was approved in 2000. After that, Purdue implemented an aggressive marketing campaign aimed at primary care providers. The FDA reviewer said that the company marketed OxyContin for use as a first-line therapy for chronic pain, which was "inconsistent" with standards. Initial reports of abuse and diversion started in 2000.

Possible contributing factors to OxyContin abuse and diversion include:

- Recent evidence suggests that oxycodone may be more reinforcing than morphine.
- High oxycodone content.
- Although it was initially believed that the pharmacokinetic (PK) characteristics of a CR formulation would reduce the reinforcing properties, experience has shown that defeat of the CR mechanisms is associated with abuse.
- Increased prescribing of controlled prescription drugs for pain (medical community more accepting of the use of opioids to treat pain).
- Purdue's strong marketing strategy.
- Warning against crushing may have alerted abusers to a method of misuse.
- Label language suggesting that OxyContin had lower abuse potential may have impacted product use or prescribing.

Initial FDA and company actions included a risk management plan in 2001 which contained education and outreach, labeling, new surveillance, and intervention. The label was changed to include an expanded WARNINGS section, which warned against breaking, crushing, or chewing the tablets; highlighted the potential for misuse, abuse, and diversion; specified the potential adverse events associated with misuse and abuse; and deleted language regarding reduced abuse liability with a CR formulation. A boxed warning was added, and the drug was restricted to a single adequate and well controlled clinical trial. Indications were revised to reflect the appropriate patient population.

The FDA is working on a class-wide REMS for extended-release (ER) and long-acting opioids as well as an interim REMS which will include:

- Medication guide.
- Communication plan – Dear Healthcare Professional (HCP) letter, Dear Pharmacist letter, and brochure.
- Timetable for submission of assessments.

The reviewer concluded that although the FDA and Purdue negotiated numerous revisions to strengthen the product labeling and risk management program over the years:

- Abuse and diversion of OxyContin continue to be significant public health issues.
- Availability of an ER oxycodone product with reduced abuse liability is desirable.
- The impact of a "less abusable" formulation of OxyContin on abuse is unknown.
- Epidemiologic studies of abuse will be required to assess the impact.

An FDA epidemiologist gave an overview of misuse and abuse in the U.S. using Treatment Episode Data Set (TEDS), NSDUH, and DAWN data. She said that although limitations from using such data include sampling methodologies, populations, and data that are not linked, the ratios of non-medical use of oxycodone are considerably higher for ER vs. immediate-release (IR).

She concluded:

- OxyContin and its generics have higher ratios of non-medical use than the comparator opioids – hydrocodone, fentanyl, and IR oxycodone. Hydrocodone prescriptions were considerably greater than for other opioids.
- Although there has been a minimal increase in estimated ratios of OxyContin non-medical use, actual numbers of users are increasing because the number of prescriptions is also increasing – an important public health problem.

THE PURDUE PERSPECTIVE

John Stewart, president/CEO of Purdue Pharma, said that the reformulation "helps address the deep sorrow that is caused by drug abuse and…does not overly restrict the availability of needed drugs for patients in pain…We've learned a great deal from our experience with OxyContin. We understand that while we manufacture products that bring important therapeutic effects to patients, those…can bring real risk."

Purdue said that the reformulated tablets:

- Are very hard, making them difficult to crush for abuse. It will also be difficult for them to be inadvertently crushed by patients or caregivers.
- Release oxycodone more slowly than current OxyContin tablets in a wide range of solvents.
- Do not "dose dump" in ethanol.
- Are difficult to put in a syringe or inject and are inefficient to use via smoking.
- If approved, roughly 90% of the supply chain will be reformulated product.
- Are bioequivalent to the current OxyContin formulation.
- Should be more difficult to prepare for abuse via multiple routes of administration, including snorting and rectal administration.

Dr. Craig Landau, chief medical officer (CMO) at Purdue, told the panel that the company:

- Redesigned its *in vitro* testing based on input received from the FDA advisory committee.
- Plans to simultaneously introduce all seven strengths of reformulated OxyContin tablets.
- Is not seeking labeling language regarding *in vitro* testing, "abuse deterrence," "tamper resistance," or "abuse resistance."

Dr. Landau told the panel that while intact OxyContin releases oxycodone over 12 hours, the CR mechanism of the current OxyContin dosage formulation is easily defeated. The physical crushing is very simple to do, making a powdered form available in <10 minutes, and underlies the many routes of abuse and misuse. He said that the reformulated OxyContin addresses the crushing method as well as the problem of alcohol taken with the drug.

Purdue's timeline:

- **Early 2001:** Purdue began reformulation efforts.
- **November 2007:** Initial new drug application (NDA) submitted for 10-40 mg.
- **May 2008:** First FDA advisory committee (rejected).
- **October 2008:** FDA completed response letter.
- **March 2009:** NDA resubmitted for 10-80 mg *in vitro* study program.
- **September 2009:** Second FDA advisory committee.

Pamela Bennett, a registered nurse and Purdue executive, explained Purdue's programs aimed at addressing prescription drug abuse:

- Detecting abuse and diversion: Researched Abuse, Division, and Addiction-Related Surveillance (RADARS) system.
- Advancing prescription monitoring programs (PMPs): 40 states have enacted PMPs.
- Training >62,000 law enforcement and healthcare professionals.
- Making unrestricted education grants to healthcare professionals and reaching >1.2 million healthcare providers.
- Building public awareness with Partnership for a Drug-Free America and the "Medicine Cabinet" public service campaign.

The science

Dr. Landau explained the polyethylene oxide (PEO) excipient which Purdue used to develop a bioequivalent reformulation. PEO is inert and found in many foods and pharmaceutical agents. It is an ideal excipient because when subjected to a certain manufacturing process, it gets hard and hydrogels in small volumes of water. It is the absorption of water that allows the company to produce the tablet. The molecular weight used in the formulation is 4 million. PEO is found in many common foods and prescription medications, including Procter and Gamble's Pediatric Vicks Formula 44m Cough and Cold Relief Liquid and Cough and Chest Congestion Relief Liquid.

Important properties of polyethylene oxide:

- Slow water uptake by PEO makes it an ideal excipient for CR formulations.
- After treatment via a specific manufacturing process, PEO confers tablet hardness.
- PEO has been safely used in oral medications for decades.

Dr. Stephen Harris, executive director of clinical pharmacology at Purdue, said that six pivotal human studies and two dose-proportionality studies demonstrated bioequivalence of the two formulations:

- Therapeutic equivalence of the current OxyContin and the reformulated OxyContin was demonstrated by fasted and fed bioequivalence at 10 mg, 40 mg, and 80 mg tablet strengths.
- Dose-proportional oxycodone exposures demonstrated across the full range of reformulated OxyContin tablet strengths (10 mg, 15 mg, 20 mg, 30 mg, 40mg, 60mg, and 80 mg).

Abuse behavior and study design

Edward Cone, PhD, an adjunct professor of psychiatry from Johns Hopkins University and an independent consultant, explained how he helped design the company's *in vitro* testing. He said that recreational abusers of OxyContin preferred insufflation as a route of administration in 2008.

Abusers typically manipulate tablets using scrapers, kitchen graters and grinders, pill cutters and crushers, mortar and pestles, and electric appliances. Chemical procedures include simple extraction using aqueous solvents, alcohol, and acids. Advanced extraction is done with pH adjustments and organic solvents. Purification is done using liquid, precipitation, and filtration. Administration tools are either oral (swallow or crush), insufflation (credit card, straw), rectal (needleless syringe), and smoking (foil, lighter).

Principles of abuser behavior:

- Although a few individuals will go to unusual lengths, most prefer fast and easy methods of tampering.

Routes of OxyContin Abuse

Route of administration	n=896
Snort	74%
Swallow	55%
Chew	34%
Inject into vein	21%
Smoke	11%
Inject subcutaneously	5%
Other	1%
Recreational abusers	
Insufflation	55%
Oral	35%
Rectal injection	9%
Abusers entering treatment	
Oral	72%
Injection	17%
Insufflation	11%

- A bigger dose and a faster delivery mode are the desired goals.
- A "resistance" barrier to tampering consists of time x effort x resources.
- As the barrier to tampering increases, the frequency of tampering diminishes.

Dr. Cone said that Purdue's *in vitro* testing was scientifically rigorous and simulated relevant "real world" abuser tablet manipulations. He advised Purdue to:

- Identify current and potential physiochemical tablet tampering methods employed by opioid abusers.
- Ensure design scope was broad enough to anticipate creativity of abusers.
- Provide input on how to translate "real world" abuser tablet manipulations into reproducible lab methods.
- Use analytical and methodological details that ensure high scientific validity, accuracy, and reproducibility.

Dr. Cone said that Purdue designed a series of rigorous studies that:

- Tested all dose strengths.
- Took them to the failure limit.
- Examined high and low temperatures.
- Extended measures: 18 and 24 hours.
- Made comparisons to current OxyContin.
- Statistically calculated replicates.
- Validated methods.
- Conducted tests in independent laboratories.
- Ensured blind conditions.

The studies examined:

- Crushability: cutting, grinding, powdering.
- Dissolution.
- Effect of alcohol on "dose-dumping."
- Extraction (simple and complex methods).
- Injection (syringeability and injectability).
- Nasal insufflation (snorting/sniffing).
- Smoking.

Dr. Cone summarized, "This does have real-world significance in looking at how people do it in the real world."

Lab test results

Judy Lee, PhD, senior director of analytics/pre-formulation at Purdue, said that the company replicated "real world" tablet manipulation scenarios in the lab. Studies were outsourced to contract research organizations (CROs), and Purdue transferred testing methods to CROs. CRO analysts were blinded to samples to the extent possible. Outside consultants conducted CRO site visits and helped interpret data. Quality assurance and statistical analysis were also performed externally.

Goals:

- **Abuse:** Simulate expected abuser approaches to intentionally crush or fragment tablets to swallow, insufflate directly, or add to solvent to extract oxycodone.
- **Patient error:** Understand the likelihood that tablets can be accidentally crushed by patients or intentionally crushed by caregivers with a pill-crusher or knife.

Summary of *in vitro* findings shows that reformulated OxyContin tablets:

- Are difficult to crush.
- Release oxycodone more slowly than current OxyContin tablets in a range of solvents, even when reduced to particles.
- Do not "dose dump" oxycodone HCl in ethanol, even when reduced to particles.
- Are difficult to inject via an insulin syringe.
- Release oxycodone inefficiently via vaporization.

Dr. Lee said that tests showed that reformulated OxyContin was difficult to crush with 16 tools. She concluded:

- Many household tools cannot crush reformulated OxyContin but can crush current OxyContin. Four of the 16 tools tested created fragments, shavings, slices, or fine particles, but never fine powder.
- Reformulated tablets are hard, require time and effort to reduce their size, and have a graded response to any form of tablet manipulation.
- Current OxyContin tablets are crushable and have a binary response to any form of tablet manipulation.

Studies 2 and 4 simulated the scenario of an abuser attempting to extract oxycodone using small volume extraction in solvents. Three solvent types were used: ingestible, non-ingestible, and pH buffers. Room temperature and elevated temperatures were used, and the time period was from 10 minutes to 18 hours. Agitation was also used. Solvents were selected to cover a wide range of chemical properties: polarity, ionic strength, and pH. The results showed early release of oxycodone from the reformulation is slower or similar to current OxyContin.

Conclusions:

- Smaller particles release oxycodone faster than large particles.
- At time points tested that are relevant to abusers, the reformulation releases oxycodone more slowly in all effective solvents tested.

The company used the 10-minute mark as the time period "relevant to abusers," but it appeared as if a lot of oxycodone was released by the 18-hour time point.

Tests looking at whether reformulated OxyContin would "dose dump" oxycodone in a simulated scenario of patients taking tablets together with alcoholic beverages showed that dose dumping did not occur. This held true across bands and strengths.

Tests looking at whether reformulated OxyContin tablets could be injected using an insulin syringe showed that reformulated OxyContin is difficult to put in a syringe or inject. Dr. Lee concluded, "Reformulated OxyContin is resistant to intravenous use."

Tests simulating oxycodone release through smoking showed that it didn't work very well.

Interpretation of lab tests

Dr. Edward Sellers, a pharmacologist from the University of Toronto, interpreted the *in vitro* findings:

- ➢ Public health benefits to patients are clear because medication errors are less likely to occur due to crushing by patients or well-intentioned caregivers, and patients will not accidentally chew it.
- ➢ Reformulation brings important incremental public health benefits for non-patients because misuse and abuse are likely to decline.
  - The harder the tablet is, the less likely the behavior.

- The tablet is more difficult to crush or easily chew.
- Reduction also is likely in intravenous and insufflation abuse.
- For those seeking a delayed effect, impact on intact oral abuse is likely to be limited.

➢ Reformulation offers an overall improvement in the safety profile across all routes of administration except intact oral.

➢ Reformulation offers an overall improvement in safety profile across at-risk populations:

- **Accidental misusers:** More difficult to defeat CR mechanism by chewing.
- **Experimenters:** Likely reduction in casual use and acute dose deaths.
- **Recreational abusers:** Likely to shift drug choice, reducing OxyContin's role as a gateway drug.
- **Sophisticated addicts:** Likely to switch due to increased time and effort. However, effect will be possibly modest on highly motivated abusers and traffickers.

Dr. Sellers said that epidemiologic studies are needed, "We can be pretty confident that the changes in formulation are going to move the safety and the public health implications in the positive direction. What we can't predict is exactly how far this positive change is going to occur. Purdue asked me if they should do *in vivo* studies in order to bring greater certainty about the change (due) to this formulation. For an approved product for which there is a public health problem, you'd generate more data, but you wouldn't be able to predict the size of the change. They wouldn't learn anything…There are going to have to be epidemiologic studies to address that. We can't answer (what percentage) improvement there will be…The implications of the *in vitro* testing are that we have examples of patients inadvertently doing things like crushing …and this has resulted in misadventure. I'd categorize those as accidental or misadventure…It is clear that the new formulation is going to change that. The non-patient group is the abusers. The harder the tablet is, the less likely that tampering is going to occur. If it's more difficult to crush or dissolve, it will be more difficult to abuse. Because of the gelling properties, there will be a big deterrent to (putting it in the nose or injecting it)…There is some abuse of the intact existing formulation of OxyContin. Hard-core abusers tamper with it. Some people take the CR because of a long-term effect. This formulation will not address that, and it will always be an issue with the CR product…What I think is going to happen is that there will be no impact of the new formulation on the abuse of the intact product, but we can be pretty confident that there will be a directional change with respect to crushing, rectal use, smoking (might not be too big an effect), injection, extracting…We will see an improvement. For patients, there will be no accidental crushing. This tablet is just too hard for that."

He said that accidental misuse and experimenting will decrease in recreational abusers because they "generally don't want to put much work in finding a drug to abuse, and they will either stop, reduce, or shift to another drug. The hard-core addicts who take pride in defeating any technology are few. This group will also shift its patterns of abuse, and I think what you'll see is a positive impact on this group, but it will be the more resistant group…The vast majority, at least 70% of abusers, are not in this group…Abusers prefer IR dose forms; 80% of abuse of opioids is with IR dose forms or those easily converted to IR. The new formulation is better for the patient from the public health point of view. It is my opinion that if this is approved, it should have a positive health impact."

OPEN PUBLIC HEARING

Twelve public speakers commented on or spoke in favor of the new formulation, and five spoke against it:

PRO

Mary Bennett, director of advocacy for the non-profit American Pain Foundation, told the panel that millions of Americans are not receiving appropriate pain care. She asked, "Should illegal and criminal activity dictate the care for others? Should people with pain who are using medications as directed be victimized by illegal use and accidental overdose?" She asked the panel not to "abandon those who benefit from around the clock, long-acting opioids and the new formulations which have been proven to be safe and effective and have the potential to reduce the risk of diversion and abuse." She urged the panel to recommend approval of the reformulated OxyContin.

Dr. Don Bivins, medical director of Good Samaritan Hospice and a pain patient from southwestern Virginia, said that because of the legal ramifications of the the misuse of OxyContin, doctors in his area are "reluctant to prescribe any analgesic stronger than hydrocodone and are more reluctant to prescribe long-acting opiates." He said one result of the OxyContin misuse is now the under-treatment or lack of treatment for patients with legitimate pain disorders, and he urged the panel to recommend expedited approval of the new formulation.

Maggie Buckley, who has Ehlers-Danlos syndrome (EDS), a painful genetic connective tissue disorder, said that she depends on long-acting opioids as an important part of her pain management arsenal. She said that she "felt like dying" after a hip dislocation, which forced her to stop working. A long-acting opioid "saved my life."

Charles Cichon of the National Association of Drug Diversion Investigators (NADDI) said that his organization works against prescription abuse and diversion. He said that Purdue is a leader in the area.

Fred Brason, representing Wilkes County NC's substance abuse task force, said that his county is probably first in the nation in terms of deaths due to misuse and abuse of OxyContin, "Just because somebody is doing something illegal, we can't take it away from people who need it. I have 41 people in my county who died last year – some misusers and some abusers."

Greg Bogdan, PhD, director/medical toxicology coordinator for the RADARS system, said that the system will be able to monitor changes in abuse rates of OxyContin.

John Carney of the Center for Practical Bioethics, Kansas City MO said that pain is subjective, and a balanced policy is needed to weigh how pain patients are treated.

Dr. Michael Clark, a psychiatrist, pain specialist, and board member of the American Society of Pain Educators, said that his organization supports continued access to CR opioids. He said that efforts to minimize conversion from long-acting CR to IR will help prevent abuse. Dr. Clark said that OxyContin has been an effective medication and urged the panel to recommend approval of the new formulation.

Penny Cowan, the founder of the American Chronic Pain Association, a pain support group, said that while safety is a number one concern, "access to care and preservation of dignity must be preserved." She spoke against a national registry, saying that it would not protect patients' privacy rights. Instead, she recommended education about pain and pain drugs. Cowan also said, "Certification of prescribers and dispensers should be consistent with the current FDA rules. Limiting access to care and treating people with pain like criminals does not address the problem facing the nation today."

Lennie Duensing, director of the American Academy of Pain Management, said that comprehensive treatment for pain must include opioid analgesics. She said that over the years she has taken suicidal calls from patients with unbearable pain.

Lisa Fowler, PharmD, of the National Community Pharmacists Association told the panel that an automated standardized REMS that can be integrated with pharmacies is essential and that any state and drug enforcement agency (DEA) licensed pharmacy should be eligible to dispense opioid products. She added that a system to dispose of unwanted drugs will result in fewer diverted and abused prescription drugs.

A nurse representing the Hospice and Palliative Nurses Association said that she is deeply concerned about some unintended consequences that may occur from a REMS. She said that although other drugs could be used, elderly people in hospices need access to a full complement of opioids, and she spoke against restricting access.

CON

Larry Golbom, **an outspoken OxyContin opponent**, lashed out at Purdue for the "opium epidemic in the U.S.," saying, "Thousands continue to die with OxyContin in their bodies." He claimed that he had in his hand the formulation, which he said can be obtained on the internet. He said that the reformulated OxyContin "can be put in the oven to separate out the active ingredient…The formulation is probably more dangerous than the original OxyContin just by putting it in the oven." He asked the FDA if Purdue had told the Agency about the oven, charging, "Purdue has continually misled America. I hope we find out today who is running the FDA − a drug company which continually brings embarrassment to (the FDA) or a legal drug cartel?"

Steve Hayes, who runs a medical addiction treatment center and is a co-sponsor of Golbom's Ban OxyContin petition, said that Purdue made it more difficult to abuse but did not make an effective blocker. He mentioned Purdue's past and asserted that the company should not be trusted, "You are going to have people who are addicts, first-time users, who are going to take this pill, and they're going to be told that they're going to get a buzz. They'll (take multiple tablets), and you'll have the unintended consequence of overdose… The drug, I guarantee you, will be marketed as tamper-resistant. Is it time for more people to die because they take this drug?"

Paula Hayes, speaking on behalf of a woman whose son died from an overdose of OxyContin, told the panel that Josh's doctor prescribed OxyContin for a back injury, "OxyContin took hold of Josh by the throat and would not let go." She called Purdue's profits essentially blood money.

Ed Vanicky called Purdue's science "junk science" and called it a company without a conscience, which should have pulled the drug off the market. He told the panel not to believe Purdue and warned that the new formulation is probably not tamper-resistant or abuse-resistant. He said that money drives the company's motivation, and he called for a ban on OxyContin.

Pete Jackson, father of a teenager who died from an overdose of OxyContin after she swallowed one pill whole, asked, "Is the new formulation less risky for people who die after swallowing a pill whole?...We already heard the answer, no." He said that approval of the reformulation will lead to doctors feeling more confident about prescribing the drug. He told the FDA that it has failed in its mission to protect the public health, and he urged the panel to vote against recommending approval. He asked that the FDA remove OxyContin from the U.S. market. He said that Purdue should no longer

be allowed to sell a drug that caused so many deaths, "The harm from this drug far outweighs the benefits…It's too late to save my daughter, but there are many who can be saved… It's time to stand up and do the right thing. Stop the deaths and ban OxyContin now."

Panel Questions for FDA Reviewers and Company Experts

Panel member Ruth Day, PhD, director of the Medical Cognition Laboratory at Duke University – who was also a member of the 2008 FDA advisory committee – said that the new data were a huge improvement. She wanted to know if the FDA and the panel have all the data available on the comparisons between the old and new formulations. Purdue's CMO answered that the FDA has all the data, "It was our goal to present the information…in the most transparent and easily available fashion…Perhaps we can submit additional raw data." Panel member Daniel Zelterman, PhD, a biostatistician from Yale University School of Medicine, said, "I see this as a correction of an existing product, which I see in a good way."

REMS

The lack of a REMS for long-acting opioids was a big concern for some panel members including the panel chair, who voted against approval for that reason.

Asked about the status of the REMS, Dr. Bob Rappaport, director of the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP), CDER, said, "We're working on the class REMS for the ER long-acting opioid products, and we have a lot of information to go through, and that's going to take us some more time. In the meantime, we had an issue we had to address of products coming up for approval – in this class – and what would we do with them… We decided, based on the fact that there are already products out there that have risk management programs such as Embeda (King Pharmaceuticals, morphine plus naltrexone) and OxyContin in this reformulation, that it would be unfair to not approve these products with a similar risk management program or, in this case, REMS, for the newer products with an agreement...that they would implement the new class-wide REMS as soon as it is available. For Embeda, the company said it would implement the new REMS when it is available. The interim REMS consists of the Dear Doctor/Pharmacist letters and a medication guide. There are no elements to ensure safe use."

Michael Yesenko, a patient representative on the panel, asked for more information about REMS and questioned whether this would be part of the product's roll-out. He also asked whether there would be any online-training for prescribers. Purdue's CMO said that the company is working with the FDA on a REMS, which will include, "a communication plan aimed at providing educational materials for individual prescribers and various medical societies."

Asked about the content of the proposed Dear Doctor/ Pharmacist letters, a Purdue executive said that the letters would say, "It is an interim REMS, and a class-wide REMS would be coming. The message will focus on proper patient assessment, storage, handling, and where people who admit to non-medical use get the drugs." Elaine Morrato, DrPH, a professor of pediatrics from the University of Colorado, Denver, with expertise in pediatrics and epidemiology, said, "So, what you're doing (with the Dear Doctor letters) is essentially generic safety messages. If you're rolling this out to pharmacies, and you're going to have a huge conversion in six to eight weeks…they will be informed that something changed, right? What is the message sent to the pharmacists?" A Purdue official answered that the message hasn't been worked out yet.

Dr. Morrato urged the FDA to have a big say in the letters, adding, "As I understand it, it's up to the company to provide the mailing lists…There is variability in those lists, and I want to make sure that it reaches everyone." Purdue's CMO said, "We are reaching very deep…into those who prescribe short-acting opioids as well as long-acting opioids." Dr. Rappaport said that the FDA has authority to decide who gets the letters, "The patent expires in 2013, and the value is how widely everyone is converted. So, thinking ahead, those other generics with the older formulation will be on the market. What really is the risk management plan? It needs to be thought through…For the FDA, when the patent expires on the current formulation, those (generic) manufacturers have the ability to go forward with the formula correct? So you're really looking at a three-year period, unless you can prove that this really does result in less misuse and abuse…I'd like to see that be part of a committee – not just a marketing study that's done on the side – but bringing in experts and a critical evaluation of that because it will hinge on that in the market."

The Purdue executive said that he would check to see if there are new patents associated with the reformulation. Dr. Rappaport said that patents aren't within the FDA's purvue, "However, exclusivity is determined by the Agency. (Purdue) won't be getting exclusivity because they didn't do any clinical studies."

Asked what epidemiologic studies the company would design, Purdue's CMO said, "We don't know." Dr. Karl Lorenz, an internist and palliative medicine expert from UCLA, said, "Many studies attributing causality are epidemiologic in nature, and I don't think that is adequate…It's a weak causal design in the first place, and I'd like any design to account for trends, to account for differential efforts, to improve this problem in general in society…There is attribution to broad areas of abuse …not only to abusers…but to users of the entire tablet. Causal understanding on this drug's impact on abuse will require tracing the drug itself to the people who are using it. Those are prescription-level designs perhaps, but they are certainly more difficult."

Dr. Randall Flick, a pediatric anesthesiologist from the Mayo Clinic, brought up the GAO report, which described compensation and incentives for the sales force, and asked the company if it plans incentives for sales people to report abuse. A Purdue executive said that the company made changes several years ago regarding incentives "in a very dramatic way," adding, "We don't want a system in place to encourage things that are not in the best interests of the patients or the company. The levels of compensation are in line with our expectations."

OxyContin name/public image

Several panel members were concerned about OxyContin keeping its name. Dr. John Markman, a neurologist specializing in pain at the University of Rochester, said that a new name might be "an opportunity to begin anew, and it might facilitate the epidemiologic studies which need to be done."

The patient representative noted that the language Purdue used in its presentation was carefully parsed, and the patient representative wondered how the company planned to market the reformulation.

Asked if the company had thought about changing the product name, Purdue's CMO said that the company considered a new name but claimed, "We are much better off retaining the trade name. The name OxyContin is recognized as one that requires substantial care in how it's prescribed. We'd be afraid that changing the product would not only lose that recognition but might create just what we're looking to avoid…We discussed it with the Agency, and they saw it the same way."

Dr. Zelterman, the biostatistician, also asked about the name, "OxyContin has a certain cachet in the marketplace and also on the street…This is supposed to address some of the issues that took it to the street in the first place; but just a new drug application (NDA) won't (fix that). I'm confused about the benefit of (keeping) the name." A Purdue executive responded, "We considered a new name, but it draws attention to a product that has been on the market since 1976…The conversation that takes place in a pharmacy then becomes even more about what the differences are. We are working on what goes in the final package insert. We have come down on the side that there may be more discussions about the differences by having a different brand name."

Asked exactly what message would be promoted with the new formulation, Purdue's CMO said, "We have no intention whatsoever of promoting the product...We recognize that we are likely to be asked these questions by pharmacists. Physicians might call the company, and we want to be certain that we don't give anyone a false sense of security that it's anything that it's not…We can't assume that there is any reduction in these liabilities."

Asked why this is a new drug application when it uses the same ingredient, the FDA's Dr. Rappaport answered, "We're looking at the excipient, and it's been used a hundred other times before…Any changes to excipients…and it becomes a new product. There are some exceptions. The fact that it appears in other drug products is not an issue. If the excipients were the same, it would be a generic."

Lab tests

Purdue used what it called "real world" tablet manipulation scenarios to test how difficult or easy it is to crush the reformulated tablets. Sixteen common household tools were used as well as several different kinds of solvents (six simple solvents, three advanced solvents, and four buffers), and the tablets were tested at a variety of time points: 10 minutes, 30 minutes, 60 minutes, 180 minutes, 360 minutes, and 24 hours. It appeared oxycodone could be released more slowly or at a similar rate to current OxyContin, and several panel members questioned the company about that.

Dr. Lorenz, an internist and palliative medicine expert, asked about the four (out of 16) tools that were able to cut fragments, etc., from the new tablet. He was told that they were commonly available tools. At least two caused "particles." He had an exchange with the Purdue scientist about the solvents:

- *Dr. Lorenz:* "Simple Solvent 6…would show that (by) using a simple solvent and a small particle band, (plus) normal household tools, the availability would be 100% of currently available oxycodone, is that right?...If we were going to be skeptical about the ability of this to represent an advance, what is the ratio?…For the solvents normally used, what kind of ratios might one expect to achieve in the time frames you looked at?"
- *Purdue scientist:* "We characterize the rate of release of oxycodone…We know the difference between the current formulation and the reformulation."
- *Dr. Lorenz:* "It appears that there wouldn't be a difference in some of those."
- *Purdue scientist:* "In advanced Solvent 1, there are higher numbers and more efficient extraction of the oxycodone."
- *Dr. Lorenz:* "Since we're talking about titration rates instead of amounts, what rate is relevant to abuse? How much trouble is too much trouble; do we have an idea?"
- *Dr. Cone, who helped design the study, interjected:* "The simple answer is that any effort that is more than what you have to do with the existing formulation is going to have some impact. The fact of the matter is that the existing formulation takes trivial maneuvers to produce a powder, put in a solution, snort, and inject. So the bar is very, very low here, and what we see in abuser behavior is that the harder it gets, the less likely it is to happen… All of these data are directional. It's conceivable that there is a situation where the improvement may be small, but in some other areas, the impact will be quite large."

- *Dr. Lorenz (referring to the amount of time to "cook" the tablets):* "I don't mean to be contrary, but I like to make lentils sometimes, and I put a pot of lentils on the stove, and it doesn't seem like a troublesome maneuver to me… Also the company agreed to market on the basis of (abuse), but it also begs the question of how this data can be interpreted. It is an incremental advance."
- *Purdue scientist:* "That is all that we are proposing. It is substantially better than the current formulation, which is easy to break down."

Asked about the 18-hour time point in the tests, Purdue's CMO said that it was included for reference, "You're correct, should one elect to leave a tablet in a glass of water for 12 hours…For the overwhelmingly majority of the time points, the (new formula) releases more slowly and requires more time than the current formulation. When release is enhanced relative to the current formulation, it is a ratio of a very small percentage difference."

Dr. Zelterman, a biostatistician, said that he was confused by the data presented, "I don't know whether 7% is enough to kill somebody, or whether 100% is not enough to kill somebody. Even though the presentations are good, the fact is that when Dr. Lorenz was concerned about the 100%, he was told, 'Oh it's nothing to worry about,' but we don't know that...I think it's important to have that information."

Easy to defeat?

Dr. Flick, a pediatric anesthesiologist, said that in just a few minutes on the internet he found several detailed ways to defeat the product, explaining, "I don't think that any one of us expects (that) this or any formulation is going to raise the bar so high that no one can defeat it, but I would also emphasize that within days or weeks after release of this product, it will be defeated and defeated relatively simply."

Purdue's CMO agreed that the information is readily available on the internet, and the company expects information to be posted on websites which will be tracked very closely, admitting, "We have reasonable expectations. This is not a tamper-proof formulation. We don't have that technology available to us. What we have is an incremental improvement."

Dr. William Cooper, a professor of pediatrics and preventive medicine at Vanderbilt University, said that Purdue had only a few quotes in its presentation on how abusers might view the new formulation. Dr. Cone talked about Concerta (Johnson & Johnson, methylphenidate) which uses the same kind of technology discussed previously.

Dangers of new formulation

Dr. Flick said that the dose of OxyContin for toddlers is 1 mg and that the new formulation is "incredibly large" for children. He said that a child wouldn't bite it and have immediate-release, "It makes no sense to me that this is at all safer for children. Children wouldn't chew these. They would suck on them, and they would swallow them…The doses here would kill a child very quickly."

Panel Consideration of FDA Discussion Points and Questions

Question 1. Discuss whether the studies performed by the sponsor adequately characterize the physical attributes of the reformulated OxyContin product.

YES (consensus)

Although several panel members had questions about how the data were presented, and whether they had all the information they needed, the panel chair, Dr. Jeffrey Kirsch from Oregon Health & Science University – who was also a member of the 2008 FDA advisory committee – said that the company's presentation was "a great improvement." Overall, the committee said that the company had adequately characterized the physical attributes of the new formulation.

Panel comments included:

- *Dr. Zelterman, biostatistician:* "Are we asking whether there was an adequate number of studies, should there be more studies, or are we asking the sponsor to summarize the data better? The question here is a little ambiguous." On the solvent data, he said that the numbers themselves were not quite summarized correctly. Dr. Rappaport commented that he didn't think the question was unclear, "We're not asking whether they didn't present it well or thoroughly, but you could say that they didn't present it well enough or thoroughly enough to make a determination."
- *Dr. Lorenz, internist and palliative medicine expert:* "It was a comprehensive look at the tablet, and there were a great deal of data available. I wonder if it's presented so we can easily see its clinical relevance. It's possible that we don't know what to make of it."
- *Dr. Donald Prough, an anesthesiologist from the University of Texas, Galveston:* "It seems to me that it would be awfully hard to make any kind of case that the data suggest that the new formulation could be more dangerous…My interpretation of the data is that the only question is the extent to which the data demonstrate that it represents more of a barrier to abuse. Since that is the fundamental question…The answer is that it is more difficult – not impossible, just more difficult."
- *Panel chair Dr. Kirsch, anesthesiologist:* "My feeling is that the information we have been provided with does demonstrate that they take the question seriously, and there's always a new study that could be done…We all have different preferences on how to look at data, but the sponsor has done a good job of providing the data in a straightforward fashion."

- *Dr. Flick, pediatric anesthesiologist:* "I echo those comments. The data, although not well described, do answer the fundamental question. Is this more difficult than the previous formulation? I think it is. Whether it prevents misuses of the drug remains to be seen. The answer to the first question is yes."
- *Dr. Jayant Deshpande, a pediatric anesthesiologist from Vanderbilt University:* "I'm not comfortable voting yes on this."
- *Dr. Allen Vaida, a pharmacist from the Institute for Safe Medication Practices:* "If the second question weren't here, I think we'd have more debate."

QUESTION 2. Discuss whether the change in formulation affects the overall safety profile of OxyContin.

Maybe a little safer but very uncertain and a Phase IV study needed.

The panel chair summarized, "The committee has expressed concern over the overall safety of this class of drugs, which I think is appropriate. The majority believes that, except for a small subset of the patients taking these medications, this might be a safer approach, but there is enough concern over this uncertainty that the committee believes that there should be a post-marketing study that looks at the clinical outcomes of this proposed new formulation."

Panel comments included:

- *Dr. Lorenz, internist and palliative medicine expert:* "We have to ask in what population the formulation might affect the safety profile…I have a suspicion that it might affect any user. Rather simple tools seem to result in the release of the active drug in the current formulation…The other complicating factor is whether the real issues…are a function of hard-core users' manipulation of the drug, and to that extent the results would be minimal. So, if I have to give a binary response, the answer is no."
- Dr. Prough, an anesthesiologist, asked about swallowing by recreational abusers, and whether they are modified pills (dissolved) or intact pills. Dr. Cole said that it was intact pills with no modification.
- *Stephanie Crawford, PhD, pharmacy administration expert from the University of Illinois at Chicago:* "How do the routes of administration vary by population?" Purdue's CMO responded that there is uncertainty and variability amongst reports, and there is no national database that looks at preferred routes of abuse. *Dr. Crawford commented,* "There is a suggestion that it may (be safer), but there is no clinical evidence."
- *Dr. Cooper, pediatrician:* "There would be some incremental improvement in the safety profile."
- *Martha Solonche, patient representative:* "This is theoretical. We're trying to project what might happen, and so, from that standpoint it theoretically might shift the abuse curve." She asked what will happen in 2013 when a generic might be on the market, and the positive effects of a new formulation would be gone. "We're talking about a theoretical safety benefit, and it might be short-lasting." Dr. John Jenkins, director of the FDA's Office of New Drugs, CDER, said that a generic drug hypothetically could be produced as long as the FDA determines that the drug wasn't withdrawn for safety reasons, "Today the drug is still on the market. Whether four years from now we will consider that it was withdrawn for safety reasons is hypothetical. But in general, you can reference a withdrawn product."
- *Dr. Flick, pediatric anesthesiologist:* "The formulation is less important (for most populations) and probably matters very little. There was a comment about doses, and the size of doses is relevant…Very few drugs on the market in a single dose can cause death. The large doses of this drug and other sustained-release formulations of narcotics have this capacity. We might do better to focus on the size of the dose in any individual tablet or vehicle, and I wonder whether the formulation is where the focus of attention should be."

Asked whether the older product and patents and the old formulation could be used as a guide for a newer reformulated OxyContin, the FDA's Dr. Jenkins said, "Yes, but that would not preclude a generic sponsor bringing forward a new formulation that has some of these newer characteristics. They have to be bioequivalent, but they don't necessarily have to have the same CR mechanism, and in many cases they don't."

Asked if that could be the basis for clinical studies, Dr. Jenkins said that generic drugs do not have to have clinical trials; they mostly have to be bioequivalent.

Asked if clinical studies have taken place for the new formulation, Dr. Jenkins said, "No, because they are linking the new formulation to the old formulation because they have to show it to be bioequivalent to the existing formulation. The FDA determines that clinical studies are necessary for approval, and we have not felt that they are necessary for approval. It is not expected that they will gain any exclusivity. That is different from patent protection, which we honor but don't regulate."

Other comments included:

- *Dr. Zelterman, biostatistician:* "The new formulation affects the overall safety profile…but I say that with a lot of caution…And we have to make a commitment to look at post-marketing safety…We have a track record of being so wrong about it."
- *Dr. Markman, neurologist specializing in pain*, said that he is still confused about the solvent tests, and he still doesn't know if taking a certain amount of the drug will kill someone.

- *Julie Zito, PhD, a pharmaceutical health science researcher from the University of Maryland*, asked about post-marketing safety, and Purdue's CMO said that from the time OxyContin was approved to the end of August 2009, 1,460 cases of tampering existed, with 85% related to abuse and 15% related to medication errors or maladministration. There was accidental drug intake by six children, six incorrect routes of drug administration, 19 accidental overdoses, 25 medication errors, 19 accidental exposures, 84 wrong techniques in drug usage process, and 89 drug administration errors. He said that any misadventure that includes chewing a tablet is less likely to occur with a product that is harder to crush.
- *Purdue CMO:* "I want to urge the (FDA) to maintain a public archive, not only of the entire proceedings but also a publicly accessible summary of these kinds of events." Dr. Rappaport said, "Our transcriber is here taking every word, and the proceedings are always available."
- *Dr. Morrato, PharmD:* "A post-marketing study and surveillance is very important…since we're making hypothetical leaps here…and perhaps a requirement for post-marketing surveillance."
- *Dr. Vaida, pharmacist:* "We're not talking about a lot of other errors that happen out there with opioids. This is a small percentage of errors, of patients chewing the tablet. From a safety profile, this is a small fraction of errors."

QUESTION 3. Should this application for a reformulated OxyContin be approved?

VOTE: 14 YES, 4 NO, 1 Abstention

The abstention was the psychologist, Dr. Day, and the no votes were two anesthesiologists (Dr. Flick and Dr. Kirsch), a patient representative, and a pharmacy professor (Dr. Zito).

Asked how to vote, Dr. Rappaport said, "You don't have to believe that the new formulation is safer. But our standard…is that the benefits outweigh the risks."

In his summary after the vote, the panel chair said that panel members had great concern for the families who have suffered great pain or loss because of inadvertent use of the drug. The committee overall felt that the new formulation is not necessarily safer, but that there is less chance of poor outcomes due to manipulation. There was a lot of concern regarding the lack of a REMS; most panel members agreed that the REMS is very important.

Dr. Markman, a neurologist, said that the public testimony about the efficacy of OxyContin was very powerful, but he was still concerned about brand identity, "In my mind, the widespread adoption/success of the use of this medication was initially associated with an unfounded claim of safety. There has been a lot of unintended harm but also some benefit because patients have obtained relief with OxyContin…Some patients have a compelling fear of opioids...and are too afraid to take them. They are afraid of issues of misuse, abuse, and diversion, even though…it is their best option for relief…Not changing the name here will continue to make that part of my job harder. This is, in fact, a new product and is addressing a vulnerability of the previous formulation."

Other comments included:

- *Dr. Cooper, pediatrician:* "The standard to think about is to decide whether the benefits outweigh the risks, and I think about the old formulation vs. the new formulation. Given the risks of the old formulation…the clear need for post-marketing studies…I feel comfortable."
- *Dr. Richard Denisco, an epidemiologist from the National Institute on Drug Abuse, Bethesda MD:* "It comes down to the one thing that's changed is the excipient, and we're being asked to approve this reformulated OxyContin. Since the only thing that has changed is the excipient…is the new formulation better than the old? We're not voting on the class of drugs…I think there are some implications with the name…This issue gets confusing…This whole issue still goes around a little bit…I'm going to make it simple and base it on what is changed, and is that change favorable or unfavorable to the public health?"
- *Dr. Flick, pediatric anesthesiologist:* "I want to acknowledge the public comments, in particular the father whose child took a single dose of this medication and died. One of the risks that is inherent in this drug is not the vehicle... (but) the dose. The doses available in a single tablet here are very large doses, and those around the table could not take one of those very large doses." He suggested eliminating some of the larger doses. He specified that the question is whether this new formulation is approved, or the old one is left on the market. The reformulation "does represent a small advance."
- *Timothy Lesar, a PharmD from Albany Medical Center*, read a headline from ***Medpage Today*** that said the panel would vote on a tamper-resistant OxyContin. He pointed out that the headline did not say, "Panel Votes to Approve Safer OxyContin."
- *Dr. David Margolis, an epidemiologist from the University of Pennsylvania:* "(The new formulation) will be a somewhat safer product." He said that post-marketing surveillance will be very important.
- *Dr. Vaida, pharmacist:* "I don't think it's a safer product, but it may have less abuse potential." He said that he is against a name change.
- *Dr. Lorenz, internist:* "It's a problem to deal at high dose levels with multiple tablets…This is a balance between public risk and benefit…It points out the effect to which the impact of this on public health depends on the market which the sponsor seeks…making sure that the market is narrow and appropriate…It is unclear whether this drug's benefits are certain or verifiable."

- *Dr. Deshpande, pediatric anesthesiologist:* "This is a very difficult vote. The families who spoke in favor of long-acting opiates and those who spoke about deaths in their families are the two opposite ends of the spectrum in my practice…I'm having some real conflicts here because I think the drugs are important – an important part of our armamentarium – but we have to…keep a record of it… Swallowing is a significant concern for young and old patients, and how that plays into the problems associated with these medications is something we haven't looked at." He said that the panel hadn't talked about a REMS. He wants to make sure that there is a safety plan in place that is more than a Dear Doctor letter. He suggested that the request for a REMS by the majority of the committee be put in the record.
- Dr. Flick said that he understands the need for high-dose opioids in some patients but added, "There is a psychological barrier for the casual user…to taking one, two, three, or four of these tablets as opposed to taking a single tablet. Very few of the uninitiated would believe that taking a single tablet of a prescription medicine is potentially a fatal dose." He said that the problems with OxyContin have come less from its formulation and more from its marketing by Purdue, "We have very little reassurance and very little information brought to us today that would inform the committee that there is substantial change and an expectation that this will not happen in the future…I don't know if we have a clear REMS that we can look at and comment on…So, I find it difficult to answer in the affirmative the question whether this should be approved. We're forced into a position of saying that we either stick with the old or go with the new. Clearly the old is worse than the new, although I think the difference is relatively small."
- Several other panel members reiterated their desire for a post-marketing safety study.
- *FDA's Dr. Rappaport:* "It's very unclear…what kind of study to do…I'm not saying that we don't agree with you, but for us to mandate or require a study, we have to know what that study is so that we can tell the sponsor at the time of approval. There are a number of groups looking at this and trying to come up with a proposed protocol for this type of study, but I think that's a ways off."

Post-vote panel comments:

- *Dr. Zito* found it difficult to vote yes because of the benefit vs. risk. She also wants a name change.
- *Dr. Deshpande*, a *pediatric anesthesiologist*, voted yes, but he had a hard time with his vote.
- *Dr. Markman, neurologist:* "The risk management plan and post-marketing studies will be critical to understanding whether it is an advance."
- *Dr. Day, a psychologist*, abstained because of what she called the "incredible risk" for some people.
- *Dr. Lorenz, internist:* "While I voted yes, it only assumes the status quo. Should that change in any way, it would be a definite no."
- *Dr. Kirsch, anesthesiologist and panel chair:* "I voted no, and it is unconscionable to move forward without a REMS."
- *Dr. Denisco, epidemiologist:* "On the principle of balance, it seemed this was a small incremental improvement. I am terrified by unintended consequences, over the report we heard on the internet, and how this will be reported and publicized. It doesn't matter if we hear tomorrow on the news that OxyContin is safer."
- *Dr. Morrato:* "I add my concern also in terms of what gets actually communicated vs. what is on the label. I think when given the choice between what's existing on the market and doing nothing, I'm afraid the class REMS will take too long to make a difference."
- *Deborah Shatin, PhD, a health researcher with Shatin Associates:* "The post-marketing (studies) and the REMS will be extremely important. Hopefully, it's not worse than what is on the market."
- *Patient representative:* "I'm horrified that there is no REMS and (at) the lack of safety presented by the sponsor."
- *Dr. Flick, anesthesiologist:* "I voted no. The sponsor did a good job of presenting the product, they did good work, and they came here in good faith. The new formulation does do what they set out to achieve. Unfortunately, by approving this drug, we lose leverage. We can't have them come back with a REMS or ask them to reduce the dose availability. For that reason, I reluctantly voted no realizing that the old formulation would have remained on the market."

♦