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by Lynne Peterson

SUMMARY

♦ Pain Therapeutics/King Pharmaceuticals' Remoxy XRT (oxycodone CR) got a mixed review from an FDA Advisory Committee which didn't consider it very abuse-resistant and recommended against an abuse-resistant label if the FDA does approve it.

♦ Alpharma's abuse-deterrent Embeda (morphine CR + naltrexone) – which will soon belong to King Pharmaceuticals – fared better with the panel. Panel members judged it to be an incremental step forward, making FDA approval likely.

♦ Overall, the FDA remains eager for abuse-resistant or abuse-deterrent formulations of opioids, but the Agency is reluctant to give a product that kind of label. The FDA sought – and got – guidance from the panel on standards for judging these products: studies of more potential abuse methods, more real-world studies, and careful labeling. Another very clear message from the panel: There should be a single risk management program for all opioids, not separate ones for each.

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FDA REVIEW OF ABUSE-DETERRENT AND ABUSE-RESISTANT OPIOIDS

Gaithersburg, MD
November 13-14, 2008

An abuse-deterrent less abusable oxycodone may be a great idea, but an FDA panel wasn't convinced Pain Therapeutics/King Pharmaceuticals' Remoxy XRT (oxycodone hydrochloride controlled-release, or PTI-821) fits that bill. The next day the same panel was more positive about Alpharma's abuse-deterrent Embeda (controlled-release morphine + naltrexone).

On November 13, 2008, the FDA's Anesthetic and Life Support Drugs Advisory Committee and the FDA's Drug Safety and Risk Management Advisory Committee met together to review Remoxy XRT – in five capsule doses: 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg, all BID – for the treatment of moderate-to-severe chronic pain. In an informal poll, the panel voted 11 to 8 that Remoxy is less abusable than Purdue Pharma's OxyContin (oxycodone hydrochloride), but the FDA views that as a neutral vote, and the panel members had a number of concerns that are likely to impact the FDA's final decision. One concern is that Remoxy may raise new safety issues such as lung damage from inhalation or death from injection. If the drug is approved, panel members recommended against giving it a preferential label.

On November 14, 2008, the same committee reviewed Alpharma's Embeda. Shortly after the panel meeting, Alpharma agreed to be acquired by King, so Embeda as well as Remoxy will both become King drugs. About two-thirds of the panel agreed that Embeda is at least an incremental improvement over existing extended-release morphines. Noting that abuse of morphine is less of a problem than abuse of oxycodone, the panel seemed to favor approval of Embeda.

In addition to recommendations on both these drugs, the FDA was seeking guidance on how to evaluate abuse-resistant and abuse-deterrent formulations and how to label them so that patients and prescribers are not misled and so that drug addicts don't get information that would help them defeat the abuse-prevention measures. The panel's advice was: study the abuse deterrence in more ways, limit labeling, and go slowly.

The FDA appears skeptical about ***any*** proposed abuse-resistant or abuse-deterrent approach. Quite simply, the FDA doesn't want another debacle like the one surrounding abuse and over-promotion of OxyContin. FDA officials are very concerned about trading a known problem (OxyContin) for a new, unknown, and potentially even worse problem.

An estimated 5.2 million Americans age 12 or older use pain relievers non-medically in a year, and one in 20 high school seniors has tried oxycodone in the past year. Among adolescents age 12-17, 3.3% were estimated to engage in non-

medical use of prescription-type psychotherapeutics. About 200,000 hospital emergency room visits are due to non-medical use of opiates/opioids.

OxyContin drug abuse and diversion are well-known to law enforcement, abuse treatment centers, and healthcare professionals. Abusers can quickly and easily extract large amounts of oxycodone by simply breaking or crushing OxyContin tablets, which disrupts the drug's time-release mechanism, allowing the abuser to immediately ingest, inhale, snort, or inject a larger dose of oxycodone than was originally intended.

Experts have warned that the same abuse-avoidance approach will not work for every opioid because different drugs are abused differently. For example, non-injectable hydrocodone isn't helpful because people don't illicitly inject hydrocodone. Thus, a single formulation is unlikely to be effective against all types of abuse.

The FDA recognizes that the abuse of prescription opioid products is a growing public health problem in the U.S., and as a result, the Agency has encouraged drug companies to develop novel interventions to prevent this abuse. However, Dr. Bob Rappaport, director of the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) in the Office of Drug Evaluation II, Center for Drug Evaluation and Research (CDER), told the panel, "Unfortunately, successful new formulations have been elusive due to difficulties related to manufacturing, biopharmaceutical concerns, and clinical failures in early studies."

In January 2002 the Anesthetic and Life Support Drugs Advisory Committee advised the FDA that opiate analgesics are an essential component of pain management and any risk management program that restricts use may compound this problem. "Risk management plans should be flexible and focus on interventions at multiple levels," the panel advised. Since then, all generic extended-release oxycodone products that the FDA has approved have had a risk management program.

Once burned twice shy might be a good way to characterize the FDA in several areas, including opioid drug labeling. When the FDA first approved OxyContin in December 1995, it allowed labeling language that (1) described a lower abuse potential due to the controlled-release formulation, and (2) noted that crushing of the tablets would disrupt the controlled-release properties. In July 2001, that lower abuse potential language was removed. The FDA believes that there are still multiple indices indicating that abuse and diversion of the current approved formulation of OxyContin continue to be significant public health issues. However, earlier this year this same joint FDA advisory panel rejected a reformulated version of OxyContin because members were not convinced it was sufficiently tamper-resistant.

In the FDA briefing documents, Dr. Rappaport told Advisory Committee members in advance of the panel:

- "To date, the Agency has been quite clear with companies that are developing these types of products that we would not entertain any change to a product's label that would incorporate a new claim of abuse resistance without **long-term epidemiological data from community-based observational studies** that document changes in abuse and addiction and the consequences of those behaviors."
- "While awaiting data from community-based observational studies (which may take a lengthy interval to collect),

Abuse-Reducing Opioid Formulations in Development

Company	Drug	Generic	Technology	Status
Abuse-Resistant Formulations in Development				
Akela Pharma	Edacs	Opioid CR	Difficult to crush, chew, extract	Phase I
King Pharmaceuticals/Acura	Acurox	Oxycodone IR + niacin	Becomes viscous	Phase III
Neuromed Pharmaceuticals	OROS hydromorphone	Hydromorphone CR	Difficult to crush, extract	Phase III
Pain Therapeutics/ King Pharmaceuticals	Remoxy	Oxycodone CR	Viscous gel	FDA advisory panel not positive
Purdue Pharma	OxyContin (new formulation)	Oxycodone CR	Abuse-resistant physical properties	FDA advisory panel voted against approval
TheraQuest Biosciences	TQ-1015	CR broad-spectrum opioid	Difficult to crush, melt, extract	Phase I
Abuse-Deterrent Formulations in Development				
Alpharma/ King Pharmaceuticals	Embeda	Morphine CR + naltrexone	Sequestered antagonist	FDA advisory panel favored approval
Collegium Pharmaceutical	COL-003	Oxycodone	DETERx anti-chewing	Phase II
Elite Pharmaceuticals	ELI-216	Oxycodone CR + naltrexone	Sequestered antagonist	Phase III
King Pharmaceuticals/Acura	Acurox	Oxycodone IR + niacin	Niacin	Phase III
Pain Therapeutics	Oxytrex	Oxycodone IR + naltrexone	Ultra-low-dose antagonist	Phase III
Shire/New River Pharmaceuticals	NRP-290	Hydrocodone IR	Prodrug	Phase II but may be abandoned
TheraQuest Biosciences	Tramadol ER QD	TQ-1015 and TQ-1017	Viscous gel in solvent	IND filed, orphan drug status for HIV neuropathy

we have also stated that we would include **data regarding the physicochemical features** of the formulation in the product label ***if*** there were sufficient data indicating that the formulation would be resistant to manipulation, so as to allow limited promotion of these features to prescribers and patients."

- "Labeling would have to be carefully crafted so as to **avoid the publication of a roadmap** describing how to defeat these (formulation) changes and with the realization that there is no perfect formulation that can resist all forms of tampering."
- "What we have not been able to provide is a clear paradigm for what would constitute a **reasonable level of abuse-resistant features** so as to merit these label changes. While on face it would seem that even incremental changes to reduce abuse might be valuable and might result in labeling that would include this information, one could question whether healthcare providers would then be under the misconception that these products are no longer abusable; or even that, because they are different from earlier formulations, they no longer carry significant risks of addiction or overdose."

In opening remarks to the joint panel, Dr. Rappaport indicated that the FDA is concerned that abuse-resistant or abuse-deterrent strategies for opioids could provide a false sense of safety, could simply cause abusers to switch to another abusable drug, and could provide abusers with new information on how to abuse a drug. He said, "Numerous companies have put extensive resources into developing these (tamper-resistant formulations that are less easily abused and perhaps less likely to result in overdose if abused). Unfortunately, the development has proven more challenging than any of us would have thought back in 2001. And we really don't have any idea of what the impact of a novel tamper-resistant formulation would be on abuse and misuse in our society…If a product reduces the ability to extract pure opioid, will it also provide the key additional label that protects the young recreational drug user from an overdose? And will it prevent fatalities in legitimate patients?...If it only prevents the hard core abuse potential, won't abusers then simply turn to one of the other abusable narcotics as they have in the past when access to an abused drug has been restricted…(Are we required) to assure that no one can abuse these products? How do we measure a product's abusability and its impact on abuse in the community?"

Dr. Rappaport said it is clear that better ways to address this public health crisis must be found, but he added, "We also must maintain access to these important drugs for legitimate patients…The advances in pain management must not be eroded. So, how do we walk the fine line between continued access to patients in pain while reducing the abuse of prescription opioids? Tough question."

PAIN THERAPEUTICS/KING'S REMOXY XRT

(oxycodone hydrochloride controlled-release, or PTI-821)

Remoxy XRT, if approved, would be sold in the U.S. by King Pharmaceuticals. It is a controlled-release oral capsule form of oxycodone in a highly viscous liquid formulation matrix with novel excipients (including sucrose acetate isobutyrate or SAIB). It is intended to be a Schedule II substance, just as OxyContin. Remoxy is designed to resist common methods of chemical or physical tampering.

Remoxy was tested under a Special Protocol Assessment (SPA) with the FDA, which generally means that a product gets approved if it meets the criteria in the pivotal trial. However, the abuse potential of oxycodone, the history with OxyContin abuse, the possibility that Remoxy could create new abuse/safety problems of its own, and the lack of data in abusers led to a split vote by the panel which left the impresson that FDA approval is unlikely. If approved, the panel did not appear to believe it should have a label saying it is abuse-resistant.

PAIN THERAPEUTICS/KING'S PERSPECTIVE ON REMOXY

Among the evidence in favor of the efficacy and safety of Remoxy that Pain Therapeutics highlighted were:

- Phase I pharmacokinetic testing showed no new or unusual issues.
- A multicenter, randomized, placebo-controlled, double-blind, Phase III trial (Study PTI-821-CO) in patients with pain from osteoarthritis of the hip or knee found Remoxy superior to placebo in analgesic efficacy in terms of Pain Intensity scores at 12 weeks (p=0.007).
- More than 1,800 patients have received at least one dose of Remoxy.
- Long-term safety was demonstrated in Study PTI-821-CM with 469 patients over 6 months and with 381 patients for 1 year. There were no clinically meaningful effect on laboratory safety tests, physical examinations, or QTC intervals. Most of the treatment-emergent adverse events were opioid-related.

Remoxy can be crushed but not into a powder like OxyContin. The company contends it can't be chewed, crushed, snorted, or injected. *In vivo* and *in vitro* studies of abuse resistance

Common Adverse Events with Remoxy

Opioid-related adverse events	%	Non-opioid-related adverse events	%
Constipation	31.2%	Headache	13.4%
Nausea	27.7%	Insomnia	12.3%
Somnolence	16.6%	Diarrhea	11.8%
Vomiting	14.1%	Fatigue	6.8%
Dizziness	10.8%	Hypertension	6.6%
Pruritis	9.1%	Depression	6.2%

included challenge tests designed to mimic common oral, injection, snorting, and inhalation (smoking) methods of abuse.

Four *in vivo* studies of abuse resistance were conducted to assess the effect of co-administration of Remoxy and alcohol (ethanol). Those studies found no significant effects on the rate or extent of absorption of the oxycodone if Remoxy was administered with 4% ethanol or 20% ethanol. There was a "minor" increase in peak plasma concentration with 40% ethanol. If Remoxy was chewed, bucally dissolved, or physically disrupted and then followed with 40% ethanol, there was an increase in the rate of oxycodone absorption, but the increase was not associated with a defeat of Remoxy's controlled-release characteristics or dose dumping of oxycodone.

Various forms of manipulation did not result in the immediate peaks in oxycodone plasma concentration that abusers seek or which might prove dangerous in cases of accidental misuse.

Remoxy was designed to defeat the four common abuse approaches:

- **Oral ingestion.** Remoxy's controlled-release matrix is not defeated by crushing, chewing, or grinding the capsules. Remoxy's formulation is neither polymer-based nor crystalline, so it does not form a brittle or glass-like structure that can easily be defeated by crushing it (as with OxyContin). There is no dose-dumping. Even at extreme cold temperatures, Remoxy cannot be forced into a hardened state. The oxycodone in Remoxy also cannot be extracted by attempts to dissolve or disperse it in liquids or solvents.
- **Snorting.** Again, Remoxy cannot be crushed or ground into a fine-particle size suitable for snorting.
- **Injection.** The resistance to extraction of oxycodone from Remoxy's high viscosity, hydrophobic formulation makes it logistically difficult for injection abuse. The viscosity makes if difficult to load a syringe with Remoxy or to deliver the product from a syringe. Subcutaneous or intramuscular injection would be expected to depot in the tissues without loss of the controlled-release mechanism. However, injecting Remoxy into a vein could pose a serious safety threat.
- **Inhalation.** The Remoxy formulation includes components that limit the amount of drug recoverable in a vapor. Those components:
  - Have lower boiling points that present inhalation hazards to the lungs and, in some case, to the eyes. Heating for a very long time is required to drive off a minor portion of the dose.
  - Decompose at temperatures necessary for oxycodone volatilization, which decreases liberation of oxycodone vapor.

Dr. Nadav Friedmann, COO/chief medical officer at Pain Therapeutics, insisted that Remoxy "is not intended, designed, or claimed to be abuse-proof or to be exhaustively resistant against all methods of prescription drug abuse."

Michael Zamloot, senior vice president of technical operations at Pain Therapeutics, described the *in vitro* testing of Remoxy, including extractability tests in solvents such as alcohol, vegetable oil, beverages, and common household liquids. He also described the physical parameters of Remoxy, such as temperature (extreme heat as well as extreme cold), crushing, grinding, mixing, etc. In beverages and household liquids, the mean percent of oxycodone extracted was 3%-15% with the highest Remoxy dose tested (60 mg) vs. 62%-92% with the highest OxyContin dose tested (60 mg).

Dr. Friedmann described Remoxy as a BID formulation that "maintains stable therapeutic blood levels of oxycodone by use of a long T_{max} and minimal peak-to-trough variation" that "resists common methods of formulation abuse." Dr. Friedmann also discussed the *in vivo* testing of Remoxy. He reviewed the efficacy data, concluding that Remoxy was effective in reducing pain for patients suffering from moderate-to-severe pain due to osteoarthritis of the hip or knee, was effective in controlling the quality of analgesia, and results in a favorable patient response.

Efficacy Results with Remoxy

Measurement	p-value vs. placebo
Primary endpoint: Change in Pain Intensity score	0.007
Secondary endpoints not related to pain	Nss
Secondary endpoints **related to pain**	
Quality of analgesia	0.004
Global assessment	0.007
SF-12 health survey (physical component)	0.003
WOMAC pain subscale	0.02

Dr. Friedmann reviewed some of the Remoxy abuse studies:

- **Chewing.** A mastication/buccal study found the rate and peak exposure of oxycodone increased after mastication – or of holding Remoxy in the cheek – relative to the whole capsule, but remained significantly lower than the reference oral solution.
- **Alcohol effect.** He said, "There is very little change in the PK curve of Remoxy administered with water or with alcohol...Looking at individual patients, there were (very few outliers)." The C_{max} ratios of Remoxy + alcohol vs. Remoxy + water were similar. Co-ingestion of Remoxy with alcohol did not affect the shape of the PK curve and did not defeat the controlled-release characteristics of the formulation. There was no evidence of dose dumping.

Alcohol Effects

Company	Drug	Increase in C_{max} relative to drug co-ingested with water			Percent change in T_{max} at 40% ethanol
		4% ethanol	20% ethanol	40% ethanol	
Pain Therapeutics/ King Pharmaceuticals	Remoxy	- 1.01	- 1.14	1.1	+ 3%
Alpharma	Embeda (morphine sulfate)	No change	No change	2	- 55%
Alpharma	Kadian (morphine sulfate)	---	---	1.03	No change
Endo Pharmaceuticals	Opana ER (oxymorphone)	1.07	1.31	1.7	- 25%
Neuromed Pharmaceuticals	OROS (hydromorphone)	1.17	1.31	1.28	- 25%
Purdue Pharma	Palladone (hydrocodone)	1	2	6	---

- **Crushing.** A four-way PK study was conducted to determine the effects of crushing + alcohol on Remoxy 40 mg vs. OxyContin 40 mg. He said, "Oxycodone absorption and peak exposure increased for Remoxy after crushing and extraction with alcohol but remained well below OxyContin and the reference oral solution. T_{max} was slower for Remoxy disrupted (3.0 hours) than for the oral solution (1.0 hours) and twice as long as that of OxyContin (1.5 hours)."

Overall, Dr. Friedmann concluded: "Four robust *in vivo* studies showed that common methods of physical and chemical manipulation were not successful at defeating the controlled-release characteristics of Remoxy. While physical manipulations or distortions of the formulation increased the rate of oxycodone release from the matrix, Remoxy did not immediately release a significant portion of its dose (i.e., no dose dumping). The rate of rise of oxycodone exposure after manipulation of Remoxy remained well below that of OxyContin and of an oral solution of oxycodone and did not result in immediate peaks in oxycodone plasma concentration, as is desired in cases of attempted abuse."

Dr. Eric Carter, Chief Science Officer for King Pharmaceuticals (which will market Remoxy XRT if it is approved), reviewed the planned risk evaluation and mitigation strategy (REMS). He said, "It is possible that the introduction of Remoxy XRT would lead to less abuse vigilance…We intend to use our tools and tactics to prevent this from happening. Monitoring the misuse, abuse, and negative health outcomes is essential to the risk:balance. We will employ both passive and active approaches…We are committed to making this work… (And) under the new regulations, the FDA has new enforcement powers for products approved with a REMS…We believe Remoxy has met the standard for approval for the management of chronic pain. Remoxy has demonstrated the potential to deter misuse, abuse, and diversion. We believe the proposed REMS is commensurate with the risks involved and, in this setting the benefits will outweigh the risks. We believe the REMS will not be unduly burdensome for prescribers or patients who meet the conditions for labeling."

Proposed REMS for Remoxy

Education	Supply chain	Surveillance
Full prescribing information	Product disposal website	Passive: Spontaneous adverse event reports
Medication guide approved by FDA and dispensed with each prescription	Flow of materials process	Passive: Literature
Message recall study	DEA liaison	Active: Media monitoring
Dear Healthcare Provider letters	NADDI listserv/DEA website	Active: NAVIPPRO
Company-sponsored medical education	Reporting of suspicious activities	
Independent CME	Epidemiology studies	
Remoxy XRT website	Universal precautions studies	
Company training		

FDA Presentation on Remoxy

The FDA didn't appear to doubt the efficacy or safety of properly used Remoxy. The issue appeared to be giving Remoxy any kind of label that would suggest it is less abusable – a status that could allow heavy promotion and widespread use. If this happens, will abusers find a way to defeat the abuse-resistant features of Remoxy and create another public health nightmare? That seemed to be the question on the minds of FDA officials.

James Colliver PhD, an FDA pharmacologist on the Controlled Substance Staff (CSS), did not appear convinced of the non-abusability of Remoxy. His report noted:

1. Pain Therapeutics' studies only evaluated the extraction of oxycodone from Remoxy capsules when exposed to solvents for ≤1 hour, not long-term (>1 hour). He wrote, "In the absence of this information, it is not possible to make conclusions regarding the tamper-resistant properties of the formulation."
2. The matrix formulation of Remoxy capsules, because of the high viscosity, may not be abusable by intravenous or inhalation routes without further manipulation, but the company did not report any attempts or tests to demonstrate the possible conversion of Remoxy to a product suitable for intravenous or inhalation use.

Dr. Robert Shibuya, medical team leader in the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products, provided a history of Purdue Pharma's OxyContin (controlled-

release oxycodone) – the problems, labeling changes, and the risk management program. He offered no new analyses, just a history lesson.

The FDA spent a lot of the panel's time reviewing drug abuse, particularly OxyContin abuse without specifically relating it to Remoxy XRT, indicating the level of concern at the FDA with worsening the abuse, misuse, diversion situation. There was only one FDA scientific presentation.

Ping Ji PhD, a senior clinical pharmacologist in the FDA's Office of Clinical Pharmacology, CDER, challenged the abuse-resistant claims about Remoxy XRT. Using PK studies of C_{max}, she found that the extended-release characteristics of Remoxy were compromised by crushing, chewing, and buccal use:

- **Crushing.** The C_{max} more than doubled for Remoxy crushed vs. Remoxy whole. "The extended-release (Remoxy) characteristics appeared to be compromised when the product was crushed and extracted with a solvent (ethanol)."
- **Mastication.** "The C_{max} is more than doubled when Remoxy is chewed…The majority of subjects have a C_{max} much like an oxycodone solution...The extended-release characteristics appeared to be compromised when the product was subjected to mastication."
- **Buccal absorption.** "The extended-release formulation appeared to be compromised when subjected to buccal absorption."

Laura Governale, PharmD, drug utilization analyst team leader in the FDA's Division of Epidemiology in the Office of Surveillance and Epidemiology (OSE), CDER, reported on outpatient drug utilization trends of oxycodone products. She said:

- More than 42 million prescriptions were dispensed in 2007, accounting for >24% of the market.
- ~7.5 million prescriptions were written last year for extended-release oxycodone products.
- 82% of oxycodone prescriptions are immediate-release products.
- The extended-release oxycodone market has remained relatively constant at 6-7 million prescriptions for the last 7 years (18% of market).
- In terms of doses: the leading strength is 20 mg (32%), followed by 40 mg (31%), 10 mg (19%), and 80 mg (19%).
- ~5.5 million prescriptions were dispensed for both fentanyl and morphine in 2007.
- Hydrocodone products have been the No. 1 dispensed prescription drug for the past 10 years.
- General practitioners were the leading prescribers of oxycodone products (28%), followed by internal medicine (18%), and anesthesiology (11%).

Joe Gfroerer, director of the Division of Population Surveys in the Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA), told the panel that 2.8%-12.1% of people age ≥12 questioned said they used pain relievers for non-medical purposes in the past year.

Illicit Drug Use

Drug type	First illicit drug use	Prior illicit drug use for non-medical OxyContin initiates
Marijuana	56.2%	95%
Pain relievers	19.0%	---
Inhalants	10.7%	---
Tranquilizers	6.5%	0
Stimulants	4.1%	0
Hallucinogens	2.0%	65%
Sedatives	1.1%	0
Cocaine	0.6%	66%
Heroin	0	12%

Capt. Kathy Poneleit, U.S. Public Health Service and director of the Division of Facility Surveys in the Office of Applied Studies, SAMHSA, reviewed national estimates from the Drug Abuse Warning Network (DAWN). In a retrospective review of more than 10 million charts, 375,031 drug-related cases were found. From 2004 to 2007:

- Emergency room visits per 100,000 population increased overall, but remained relatively flat for illicit drug use.
- The highest number of emergency room visits were in patients aged 21-54.
- ER visits for medical use of opioids increased, but visits for non-medical use remained relatively constant.
- Non-medical visits to the ER for opioid analgesics neared 287,000 visits.
  - One-quarter of these were for oxycodone and one-quarter for hydrocodone.
  - There has been an increase over the last few years in visits for immediate and unknown release types of opioid analgesics.
- The majority of patients were treated and released.
- Polydrug use was higher for immediate vs. controlled release.
- Morphine-related ER visits were ~30,000.
  - Immediate-release drug visits increased.
  - Controlled-release visits remained relatively flat.

Capt. Poneleit said that the DAWN shows a link between ER visits and drug use and that unique names for immediate-release vs. extended-release products would enable better surveillance.

Deborah Trunzo, team leader, Drug and Alcohol Services Information System (DASIS) in the Office of Applied Studies, SAMHSA, reviewed data on admissions to substance abuse treatment for abuse of opioids, based on the Treatment Episode Data Set, which is collected by the States and reported to SAMHSA, primarily from facilities receiving public funds. She estimated that the 1.8 million annual admissions cover about 80% of admissions. From 1997 to 2006, hospital admissions for opioid analgesics increased by 367% vs. a 4% increase for heroin.

Treatment Admissions by Primary Substance (2006)

Drug type	% of admissions
Alcohol	39%
Marijuana	16%
Cocaine	14%
Heroin	14%
Stimulants	9%
Opioid analgesics	4%
Other	4%

Increase in Admissions for Specific Opioid Analgesics (2000-2006)

Drug type	% of admissions
All opioid analgesics	168%
Codeine	137%
Hydromorphone	121%
Meperidine	19%
Oxycodone	1,513%
Pentazodine	67%
Propoxyphene	- 60%

Richard Abate, RPh, a safety evaluator in the FDA's Division of Medication Error Prevention, OSE, CDER, reviewed reports of manipulation (abuse) of oxycodone extended-release products in the FDA's Adverse Events Reporting System (AERS) database. He said there were 7,300 events reported, and 380 related to oxycodone extended-release tablets. Of these, 171 did not involve manipulation of OxyContin."

Methods of Manipulation of OxyContin and Morphine ER in AERS

Manipulation method	Number of OxyContin events	Number of morphine extended-release events
Methods of manipulation (OxyContin n=114, morphine ER n=18)		
Crush	90	11
Chew	16	3
Cut	2	0
Grind	2	0
Melt	2	0
Boiling/heating	0	2
Crack	1	0
Dissolve	1	2
Methods of administration (OxyContin n=95, morphine ER n=22)		
Inject	69	11
Snort	26	2
Oral	0	8
g-tube	0	1

Cathy Dormitzer PhD, from the FDA's Division of Epidemiology, OSE, CDER, offered a summary of drug abuse "rates" in the U.S., focusing on oxycodone. She agreed non-medical ER visits appear similar for oxycodone IR and oxycodone ER, but she pointed out there are 4 times as many oxycodone IR prescriptions written than for oxycodone ER, "So, when you consider that…The number of non-medical use ER visits per 10,000 prescriptions is 7-10 for oxycodone IR and 35-38 for oxycodone ER

PUBLIC WITNESSES ON REMOXY

During the public comment period, pain groups urged the FDA not to make access to opioids more difficult for legitimate patients while several consumers challenged the claims that Remoxy is abuse-resistant and urged the FDA not to approve it.

➢ **Pro – Mary Vargas, a lawyer, vice chair of the American Pain Foundation**, a former member of an Alpharma advisory board, and a pain patient herself, urged the panel to remember the patients who need opioids, "OxyContin, fentanyl patches, and an implantable medical device gave me back my life and allowed me to have a family…but I have found myself unable to attain them. The burdens of risk management are placed directly and indirectly on our (legitimate patients') shoulders...Going into the pharmacy, I never know if I will walk out with the medications I need to care for my boys…Even a law degree and a lawful prescription are not enough to get my prescription filled…It is the reality I ask you to weigh when you consider a REMS…I don't know if a REMS program will prevent abuse and overdose in non-patient populations while assuring access is not further reduced for legitimate patients (we should take the risk)…We are the reason these medications are manufactured …The risk that our access will be further limited should matter as much as abuse by non-patient populations."

➢ **Pro – Lennie Duensing, executive director of the American Academy of Pain Management**, emphasized how many legitimate pain patients need oxycodone. She said her members support a pain management approach, but they are worried about a burdensome REMS.

➢ **Con – Marti Hottenstein of Helping America Reduce Methadone Deaths** told the panel, "I expect the FDA to consider the American public's well-being…I have two questions: (1) Was Remoxy tested on an 18-year-old addicted person? (2) Was Remoxy ever melted? I am not fooled that Remoxy is any different from OxyContin, and I hope my FDA is not fooled either."

➢ **Con – Joanne Peterson, founder of the Learn to Cope,** a support group for families grappling with addiction to heroin and OxyContin, told the panel that her son was given crushed OxyContin by an adult pain patient with a legal prescription. He went on to become a heroin addict, and several of his friends died from OxyContin abuse. She said, "I want to see

safe drugs that are not abusable…I'm sorry for people who suffer in pain…but our sons suffer, too."

➢ **Con – Ed Vanicky, who lost his wife to prescription opioids.** His wife was prescribed OxyContin after an auto accident several years ago, and she took it as prescribed, but she died from acute oxycodone intoxication. He said, "Based on a company (Pain Therapeutics) press release and online materials, I remain very skeptical that it (Remoxy XRT) will be truly abuse-resistant. I assure you...the publicity around OxyContin will only motivate the person who chooses to abuse this type of medication to work until they find a way to extract the oxycodone from Remoxy…And then we will have a more dire situation on our hands than we do now…These new drugs are not necessarily (designed) for safety but for the money they can bring (the pharmas)…I believe the real issue is not…putting more oxycodone in the hands of doctors and abusers. It is recognizing the problems with oxycodone and asking when enough is enough."

➢ **Con – Larry Golbom, a pharmacist and host of the Tampa-based Prescription Addiction radio show**, claimed the structure of oxycodone and heroin are almost identical, claiming that Remoxy is not a "modern medicine, just modern marketing." He added, "For doctors to say they can single-handedly manage this drug is the height of arrogance and incompetence…To imply that millions of people are in need of this dangerous drug is the height of misrepresentation …I've a concern that the matrix starts with sucrose – common table sugar. Where are the heat studies? What about this product past 100 degrees? It also appears the chewing and alcohol studies were done in patients with an empty stomach."

PANEL QUESTIONS FOR THE FDA AND SPONSORS ON REMOXY

Among the panel questions/issues were:

C_{max}. *Why did the FDA have a different C_{max} analysis than the company? Were both analyses based on the same data?*

FDA officials said it was the same data, but the FDA and the company focused on different parameters – and the FDA focused on a longer timeframe, not just the first few hours. A panel member said, "I'm still struggling with the time vs. concentration issue…The FDA focused on C_{max} concentration because, ultimately, that is the safety outcome…One might then be led to conclude it (Remoxy) is unsafe because its C_{max} is equivalent to drugs already out there…So, it does seem the issue of time to onset is important for us to consider…It seems it would be valuable to have an abuse deterrent formulation available. What is an adequate amount of deterrence? I'd say the sponsor has demonstrated slower onset, the amount of time to get the drug out of the matrix is slower…What is the right amount of deterrence that is an overall safety profile and also what does it really mean when you put it in the real world?… Will someone stand around with it in the cheeks for 3-5 hours? We want industry interested in making safer products, but I think we aren't working with any standard."

Dr. Sharon Hertz, deputy director of the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products, said, "That's why we are here. We don't have a standard on how much margin is safer. We don't think time to C_{max} is not important. We presented our analysis based on C_{max} to complete a picture…We are asking you how much better is better. How do we decide what is clinically important? How do we decide if something is an advance? How would you characterize that? How would you measure that? These are all questions without an answer yet."

How much individual patient variation might there be in the C_{max} of Remoxy?

Dr. Hertz said 40% of individuals could have high levels with crushed Remoxy.

Are there any clinical endpoints in vivo that doctors should be attentive to?

Dr. Friedmann said, "We don't think there are more side effects with our drug (than OxyContin)…Every drug changes with manipulation. Remoxy changes less, and in particular less than OxyContin. C_{max} or C_{max} ratios alone do not speak to dose dumping or the attractiveness of a formulation. Time to C_{max} and T_{max} are equally important."

Half-life. *What is the half-life of Remoxy?*

A company official said it is 10-12 hours or longer, supporting BID dosing.

Extraction. *Is there really a meaningful difference in extraction resistance beyond one hour?*

Panel member Dr. Sid Wolfe of Public Citizen Health Research said that it appeared that over time the same range of drug is extracted with OxyContin and Remoxy – about 50%-60%. He wanted to know why the company didn't study a longer time period. Pain Therapeutics' Dr. Friedmann didn't directly answer this, but he said, "OxyContin is 90% extracted in five minutes, and our data in 3 hours are half of that…The data we gave at 3 hours were much more rigorous…This drug is designed for patients in pain. It will deliver drug. The longer you wait, the more the drug will come out. In common methods for abuse, someone wants to get high immediately (not wait hours)."

Injection. *What are the potential toxic effects if an abuser is able to inject Remoxy?*

Dr. Friedmann said, "We believe the consequences of injecting are severe." Another company official said they had studied injections in three dogs using pre-filled syringes prepared at high temperature in the compounding lab, "Immediately prior to injection, the pre-filled syringes were heated to reduce viscosity somewhat and enable injection through a large gauge needle…There were no significant clinical observations until necropsy (at 3 days post-injection). Then, we found a significant finding – severe black foci in

multiple lobes of the lungs at all dose levels (tested), and microscopic findings consistent with primary vascular occlusions at all 3 doses tested in the lungs, and at the high dose in the heart…IV administration of Remoxy was associated with several adverse events."

Affect on competing products. ***What is likely to happen to current oxycodone products if a tamper-proof formulation is approved by the FDA?***

The FDA's Dr. Rappaport said that currently approved products might be withdrawn if and when a truly safer formulation were approved, "It is hard to know exactly, but there would have to be documented evidence of increased safety. If someone could document that with appropriate metrics – and how do you measure that? Is it improving community safety? – Then, FDA might have a reason to say to other companies – and whether we could take them off the market would be something under consideration. But first, you have to establish that the impact of the change creates a safer environment."

Risk management. ***What would the effect of a REMS be on the ability of the homeless, mental health patients, or substance abusers with pain, to get appropriate pain medications?***

King's Dr. Carter said, "Obviously, the goal of the proposal I presented…is to be as broad-based and as comprehensive as possible relative to the preventive measure incorporated into that…Essentially, what we are trying to do is to provide education, a measure of training, and some tools, and then monitor, evaluate, and interpret. One would anticipate if Remoxy is approved – if the REMS is in place with our surveillance system – we would be looking for the kind of impact in special populations and special geographic areas and, in time, provide the kinds of information you are looking for."

Labeling. ***Would Remoxy be labeled for use in moderate osteoarthritis?***

The FDA's Dr. Rappaport said, "The indication would not be the moderate pain of osteoarthritis. It would be moderate-to-severe pain….The opiates have always had a general pain claim for moderate-to-severe pain…We allowed studies performed to be put in the label so the sponsor can promote it by saying it was studied in osteoarthritis or bunionectomy patients, etc. But that is not the indication, just a way to tell prescribers in what patient populations it was studied."

Pricing. ***Could pricing be used to control use?***

Dr. Rappaport said, "We can't mandate how a company prices a drug…but as a tool to manage risk, it is a reasonable one, and one we would probably consider a beneficial addition to a risk mitigation strategy…For example, when Actiq (Cephalon, transmuscosal fentanyl citrate) was approved, they priced it so that there would be less product in the home and, therefore, less risk of exposure for certain dosages. It was an unusual pricing scheme, and I don't know if it had any impact…That was intended to prevent accidental exposure and not address these issues." The King official added, "We are trying to come up with a take-back program."

Laboratory data. ***How can a decision on Remoxy be made on mostly laboratory data?***

Panel member Dr. Richard Denisco, a medical officer in the Division of Epidemiology, Series, and Prevention Research at the National Institute on Drug Abuse (NIDA), said, "We are asked to make clinical decisions based on laboratory data. If it is possible – and it appears it is possible with enough time – to get the majority of the medication (oxycodone) out of the matrix formulation, could that not then be one more step of concentration in creating a formulation that could then be abused? Wouldn't it be just one step away from where we are now (with OxyContin). Granted it wouldn't be practical to hold a pill under your tongue for 3 hours…but if you could do that outside in a beaker or on a bench, maybe it could be concentrated if it is extracted out of the matrix at 1, 3, or 20 hours." Dr. Friedmann repeated, "This medication is designed to release drug. If you put it in solution for a long time, it will release drug in large volume…Our goal was to limit immediate gratification. A kid in a schoolyard or someone in a bar can't crush it (Remoxy) and get 90% (drug availability)…We provide at least a limited solution to that problem (OxyContin abuse)."

Real-world experience. ***Why aren't there any tests in drug abusers?***

The company was asked this question several times by different panel members. A company official said only, "We did not do abuse studies…That may be important when comparing oxycodone to morphine, but here we are comparing our drug to OxyContin – oxycodone to oxycodone. That's why we didn't think it was necessary to do that study."

Missing abuse tests – heating, skin popping, subcutaneous. ***What happens when Remoxy is heated? Can oxycodone be extracted if Remoxy is heated? Was skin popping abuse or subcutaneous delivery tested?***

Dr. Athena Zuppa, a pediatric critical care specialist from Children's Hospital of Philadelphia, said she is concerned about volatilization (inhalation) studies that found inhaling Remoxy could be very caustic to the lungs, "I'm concerned abusers will die from inhalation." A Pain Therapeutics official said the amount of drug released during volatilization was carefully measured, and only 12% was recovered from Remoxy; the rest was pyrolyzed or unremovable from the char residue. Another company official said neither skin popping nor subcutaneous abuse was studied.

Food effect. ***What is the effect of food on absorption?***

A company official said, "It is very important to take this product with food…I also considered significant food effects as an abuse-resistant feature…We expect the label to say, "Take this with food."

PANEL DISCUSSION OF FDA QUESTIONS ON REMOXY

QUESTION 1. Discuss the adequacy of the tools we have to assess the impact of a novel opioid formulation on the abuse, misuse, and diversion of the product in the community.

- *FDA's Dr. Hertz:* "It isn't so much a question of what is adequate but what are the tools needed. Do we have the tools? Do they exist? We are not asking if REMS is sufficient…In general, what is necessary to understand the impact of a change of formulation on use and abuse."
- *FDA's Dr. Rappaport:* "At this time, we are still having a lot of extensive internal discussions on how to implement a REMS, if at all, for an opioid product. There is a risk management program for most opioids…They are a panoply of surveillance and education materials...but it will take time to sort through the best way to implement a plan and to what degree…We agree it would be nice to have one over-arching program (for all opioids), but how to implement that is easier said than done."
- *Dr. Karl Lorenz, an internal medicine specialist from UCLA:* "I am concerned with the inadequacy of current systems for monitoring diversion and monitoring the initiation of new drugs with a potential for diversion. In particular, the inability to relate the denominator and the occurrence of adverse events or clinical diversion/abuse. I'm deeply concerned. I think the answers are there. I'm not sure it is our job to provide the answers."
- *Timothy Lesar, a PharmD from Albany Medical Center:* "I don't think we can do it. The ingenuity of these individuals (abusers) is very good…What happens if I chew it like chewing gum?...I see higher mortality with this drug later. Those are things that are very concerning."
- *Dr. Wolfe:* "In May 2007, Purdue Pharma agreed to pay for an outside company to do a corporate integrity agreement, which means monitoring all promotion and use… We have an existing product out there (OxyContin) which is the model – the horrible model – for extended dose oxycodone, and I would like to see some more information about what is already out there. When I hear abuse resistance – that is what Purdue said at the beginning…So, I would like to see that happening in real life with the product right now on the market, which has a corporate integrity agreement. There are data, and the one-year report that should have been finished in May or June of this year…Has anyone at FDA seen that report?" Dr. Rappaport said, no.
- *Dr. Zuppa:* "We are not talking about hours and hours of delay (with Remoxy) – just an hour…We need to think in practical terms…I'm very concerned about a medication whose primary difference is the matrix, and if the matrix is abused or misused by injection – which is difficult but possible – that injection will cause…instant death. Are we gaining anything? What is the risk:benefit ratio of this? I have severe concern after seeing the dog autopsies."
- *Sharon Walsh PhD, a behavioral scientist from the University of Kentucky:* "The standard abuse liability approach is to examine it in individuals with a history of using the drug prior to marketing and compare it to controls. We already know oxycodone is highly abusable, and they don't need to establish that. But there is a big intersection between pain and addiction. We do a fair amount of evaluation in pain and in drug users without pain and little in drug users with pain…I don't think that has to be…It's the fox in the hen house problem…It seems to me going forward, the independence of the collection procedure is important so the formulations can be compared to each other for a signal…One of the most effective tools is education…We had a company with a strict REMS and no abuse…But then you don't know if there is no abuse or if the REMS is effective…We want to think about the REMS approach scientifically – to determine the efficacy of the program and so the public can feel confident in the results."
- *FDA's Dr. Rappaport:* "There are a lot of tools out there. We talked about a lot of them – DAWN, TDS (the Drug Enforcement Administration's Tactical Diversion Squads), Florida medical examiners on overdose deaths, state prescription monitoring. Sometimes we can only know it is oxycodone and not a specific product…But sometimes we can see goo in the stomach or we have a pill or a patient's friend remembers a specific insignia… So, there are tools. Should we actually approve this or another product? Are those tools enough to capture the information we need to assess the impact on the community or is there more we need to do?"
- *Dr. Jack Rosenberg, an anesthesiologist from the University of Michigan:* "When you are making a product toward abuse prevention, it ought to be tested in an abuse-prone group prior to general release." (Several other panel members shook their head in agreement)…Several of us have raised concerns about the toxicity of the vehicle with this product…If you are looking for opioid abuse resistance you should find out what it will be doing in the abuse populations."
- *Dr. Leonard Paulozzi, a medical officer for the Centers for Disease Control and Prevention (CDC):* "When people are found dead, there is not much information about the medications they took. Less than 55% of the time, there will be a prescription in the records…To pathology, it may look like oxycodone, and they can't tell you the formulation…It will be difficult to know the risk…AERS captures some deaths but only a small fraction of the deaths in the U.S…DAWN data has the same problem; it will look like an opiate, and under toxicology it will look like oxycodone, but there is little information on the formulation. With DAWN it is very difficult to identify specific brand names…The price of the pills on the street might be a measure; if Remoxy costs a lot less than the same size OxyContin (illegally), we might have a go sign."

- *Dr. Wolfe:* "The company is claiming this (Remoxy) will be a little less abused, and if that is the case, they should have to show it. I think automatically for any opiate, there needs to be clinical trials in people who are more like abusers...and dual populations (e.g., drug users with pain)."

QUESTION 2. Discuss whether or not the available data suggest that this formulation will be less susceptible to abuse and misuse.

Although the FDA did not ask the panel for any votes, Dr. Jeffrey Kirsch, the acting chair and an anesthesiologist from Oregon Health and Science University (OHSU), conducted an informal poll of members on this issue. **The panel members voted 11 Yes, 8 No.** The industry representative, Dr. Bartholomew Tortella of Novo Nordisk, was one of the yes votes. If this had been a formal vote, he would not have been allowed to vote. Normally, the FDA considers a vote like this (11:8) to be a neutral vote that leaves the issue up to the Agency.

Panel member comments included:

- *Dr. Zuppa:* "It can be injected and when injected causes significant damage to the heart and lungs. And when you inhale it, you get as much as OxyContin, and you could damage the lungs, so I don't think it is less subject to abuse."
- *Panel chair Dr. Kirsch:* "Will that make it less abused? One would hope."
- *Michael Yesenko, a patient representative from Rockville MD:* "I don't think it is less susceptible to abuse, particularly because of Dr. Ji's report (on C_{max})...and because of the possibility of skin popping. I don't believe there are data to suggest this formulation would be less susceptible to abuse."
- *Dr. Wolfe:* "We do not have evidence it is less susceptible to abuse. It is 1-1.5 hours to T_{max}…I'm not sure that is a huge difference between these two products (Remoxy and OxyContin)...So, the answer for me is, I don't think so."
- *Harriet de Wit PhD, a psychiatrist from the University of Chicago:* "I think this is an advance…At the very least it will be more difficult and more burdensome to abuse… I've been impressed as a drug abuse researcher…There is pretty good evidence this will be less likely to be used by the drug-abusing population."

QUESTION 3. Discuss whether or not inclusion of data on the physiochemical attributes of this new formulation in the product labeling could potentially mislead prescribers or patients into thinking that the new formulation is less likely to be addictive or unlikely to be abused or result in addiction?

- *Dr. Judith Kramer, an internist from Duke University Medical Center:* "I can't imagine that the marketing wouldn't at least imply more safety…If this is marketed, there may be an assumption by prescribers that it is safer, but that hasn't been tested."
- *Dr. Rosenberg:* "One of the chemical properties of this drug is extreme toxicity on injection…Regardless of the labeling, I don't think that is enough to get people not to do it…I would not be in favor of including this in the labeling."
- *Robert Kerns PhD, national program director for pain management, Yale University School of Medicine:* "I would suggest a label should be clear about what it is not – that it is ***not*** better than other formulations."

QUESTION 4. If you believe that patients or prescribers could potentially be misled, discuss whether or not this risk is acceptable, considering the potential benefit from the changes to the formulation.

Panel member Dr. Denisco said, "It would be important for (sales) representatives not to go out and say, 'Look at this stuff. It is like rocks…You can't inject this.' That is when the trusting doctor could get bamboozled."

QUESTION 5. If you believe that this formulation is likely to reduce its abuse and misuse, discuss whether or not you recommend including any of the data in the product labeling.

- *Dr. de Wit:* "An informed prescriber will know how to interpret that."
- *Dr. Walsh:* "Any formulation, any sponsor, would not put a lot of effort into developing an abuse-deterrent formulation and then not be able to say anything about it in the package insert…Why would they spend the time and money to develop something that is helpful?…While panel members may have concerns about the relative benefit of this (Remoxy)…I'm not making the case for this formulation – it's more of a general issue."
- *Dr. Lorenz:* "For me the crux of the issue…is the difference in the endpoints that we trust – in PK or clinical endpoints. In a sense, any opinion I have is conditioned on data we have…I wouldn't say it is very inappropriate to market a drug on that basis, but we can point to many, many examples where endpoints like this turn out not to (be valid in the real world)…I think we want a better demonstration of that before we allow it to potentially result in the sea change it might cause in prescribing habits."
- *Dr. Kramer:* "I agree with Dr. Lorenz…There needs to be incentive for manufacturers to try to find something that is a better option…But if we were very specific on details on the way it is better…then we would be doing the same thing that happened with OxyContin…If we are to approve something like this, how would we express the benefit without giving it a…hook?"

- *Dr. Zuppa:* "If we are going to see a delay in the peak effect with a tampered effect, I would like that delay to be specified as one hour."
- *Dr. Wolfe:* "This is the second time this issue has come up. The first was in May (2008) with the reformulated OxyContin. I agree fully that companies should be encouraged to develop products less subject to abuse… but that doesn't mean that simply by engaging in that effort it should yield automatic approval…One could not imagine a different patient population from what will happen in the real world if this got approved from what was studied…We have no idea what this drug would do in all sorts of people excluded here…So, part of the message to anyone who wants to develop a product really less subject to tampering or abuse is that they have to study it in the right kind of population."

FDA Reaction to the Panel Discussion on Remoxy

FDA officials spoke with reporters after the panel meeting. Asked what message the FDA got from the panel, Dr. Rappaport said, "Our message is that there aren't a lot of answers to these very difficult questions I posed…We asked experts today – and at a previous meeting on reformulated OxyContin. We are not hearing a lot of good answers to the questions about what's available to measure the impact of these products, about what should go on labeling."

Asked why there wasn't a formal panel vote, Dr. Curtis Rosebraugh, director of the FDA's Office of Drug Evaluation II, CDER, said, "That wasn't the purpose of this meeting… Everyone is struggling...If there is a change in formulation, is that enough for new labeling? We wanted to see if we could find a threshold, a bar…What is the threshold someone has to have with a formulation change? And what body of evidence do they need that this is important and doesn't have a detrimental effect. That is harder with a yes/no vote. It is better in dialog."

Asked about the possibility of removing existing oxycodone products from the market if a true abuse-resistant oxycodone were approved, Dr. Rappaport said, "It depends on whether you can show with good data that there is an improvement in the abuse compared to the other products. In that case, if you had good quality data and a metric that established this product is safe and caused less abuse in the community, we would have to consider the possibility of removing the other products from the market. That is not an easy thing." Dr. Rosebraugh said, "It is not just this (Remoxy). If any product came out with less abusability and fewer problems, why keep the others on the market?...We would have to have a good metric measure and a lot of faith that they (the sponsor) showed that." Dr. Rappaport added, "We are not getting a good answer to that."

Alpharma/King's Embeda
(modified release morphine CR + naltrexone, or ALO-01)

On November 14, 2008, the FDA's Anesthetic and Life Support Drugs Advisory Committee met jointly with the Drug Safety and Risk Management Advisory Committee once again, this time to discuss Embeda, and their reaction was much more positive than with Remoxy the day before. Alpharma is seeking approval of 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg capsules taken QD or BID orally or opened and sprinkled on applesauce.

Embeda is not abuse-proof, and it is not much of an abuse deterrent, either. It can be defeated by several solvents, and the company only tested oral abusability – not IV injection or inhalation. Embeda offers some abuse prevention benefits, but is it enough to allow the FDA to remove Alpharma's Kadian (morphine ER) from the market? Probably not. However, the Embeda panel seemed to favor approval, though no formal vote was taken, agreeing that Embeda is an incremental step forward and noting that the abuse problem with morphine is much less than with oxycodone.

The amount of naltrexone in Embeda is not intended to block all or even most of the effects of morphine if the product is abused. Instead, the naltrexone is intended to block enough of the morphine effects to reduce the euphoria drug abusers seek. The drug is formulated so that there is no effect from the sequestered naltrexone when the product is taken as directed, but when it is crushed, dissolved, or chewed the naltrexone extended-release pellets cause rapid release and absorption of both the morphine and the naltrexone.

In advance of the meeting, the FDA's Dr. Rappaport wrote panel members, "While morphine has not shown a particularly high signal of abuse in recent years compared to the other potent opioids, it is clear that as we put more efforts into controlling the abuse of one opioid, abusers turn to other available products. Just to cite two examples, we have seen this phenomenon occur when heroin addicts turned to (Sanofi-Aventis's) Talwin – before it was reformulated with an antagonist – when the heroin market dried up in the 1970s and more recently with the abuse of methadone increasing as more and more oversight of OxyContin (Purdue Pharma, controlled-release oxycodone) prescribing has been instituted over the past eight years. Morphine itself has an established history of abuse resulting in addiction, overdose, and death that goes back well over a century, so it is essential as part of an overall abuse reduction program that we provide appropriate risk mitigation strategies, including the development of abuse-resistant formulations, for morphine products as we institute these changes for the other potent opioid products."

Embeda is a capsule comprised of individual pellets containing morphine sulfate with a sequestered naltrexone hydrochloride inner core. Alpharma claims that if it is taken as prescribed, only morphine is liberated in an extended-release profile to provide relief of moderate-to-severe chronic pain for up to 24 hours. The naltrexone is an opioid antagonist and is

designed to remain sequestered in the core of each pellet. However, upon crushing, dissolving, or chewing of the pellets, both the morphine and naltrexone are available and absorbed as an immediate-release dosage form. Uniquely, the released and absorbed naltrexone would:

- Mitigate the liking and euphoric effects of the morphine.
- Deter drug tampering and diversion.

Combination products comprised of an opioid + an opioid antagonist fall under special FDA regulations – each component must make a contribution to the claimed effect. Currently, there are two combination products like this, both of which contain naltrexone to deter IV abuse. However, no studies have ever been done to assess whether the addition of naltrexone to these products has resulted in a decrease in abuse.

- Sanofi-Aventis's Talwin NX (oral pentazocine/naloxone)
- Reckitt Benckiser's Suboxone (sublingual buprenorphine/naloxone).

As with Remoxy, the FDA is asking the panel to address the adequacy of the abuse-resistant features of Embeda and to consider any increased risks that might be associated with the formulation for legitimate patients.

In 2004, Purdue Pharma's Palladone (modified-release hydromorphone) was taken off the market because dose dumping occurred when ingested with alcohol. Therefore, there are currently four approved modified-release oral morphine products on the market:

- **Purdue Pharma's MS Contin** – indicated for moderate-to-severe pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time. It is available in 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg doses BID. The two highest doses have a boxed warning.
- **Oramorph SR** (generic) – indicated for the relief of pain in patients who require opioid analgesics for more than a few days. It is available in 15 mg, 30 mg, 60 mg, and 100 mg tablets BID and TID.
- **Alpharma's Kadian** – indicated for moderate-to-severe pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time. It is available in 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, and 200 mg capsules QD and BID. The two highest doses have a boxed warning.
- **Ligand Pharmaceuticals/Elan's Avinza** – indicated for moderate-to-severe pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time. It is available in 30 mg, 60 mg, 90 mg, and 120 mg capsules QD. It has a boxed warning against using with alcohol.

FDA staff searched its Adverse Event Reporting System (AERS) database before the panel meeting looking for post-marketing cases of abuse with any of these four approved drugs. They identified:

- 22 cases of improper manipulation, with the majority intentional abuse.
- The methods of manipulations included crushing, chewing, dissolving, and heating. The most prevalent method of manipulation was crushing (n=5).
- The most common route of administration was injection (n=11). Embeda is intended as an oral drug, but the FDA noted that it has only been tested with oral administration. FDA staff wrote, "Thus, it is unclear what the potential of effects (are) of injecting this product following manipulation."

FDA pharmacologist Dr. James Colliver told panel members in briefing documents that Alpharma's Embeda studies "demonstrate that under selected conditions, morphine can be efficiently extracted in isolation from naltrexone from Embeda capsules. Once extracted, the morphine could be subject to abuse by various routes of administration."

In opening remarks to the panel, the FDA's Dr. Rappaport noted that Embeda works by "a completely different mechanism than the product we discussed yesterday (Pain Therapeutics' Remoxy). Embeda contains the opioid antagonist naltrexone which is intended to reduce the euphoria abusers expect from the opioid."

He pleaded with the panel to give them the guidance that the FDA did not get at the Remoxy panel, "We need your assistance to evaluate these types of formulation changes intended to reduce abuse, what metrics should be employed to measure that...and how safely to include the information in the labeling to inform and not mislead patients and prescribers – and not provide instructions for addicts and drug dealers that will allow them to more easily overcome the changes to the formulation."

Dr. Rappaport said the FDA recognizes that these are tough questions (that the agency is posing to the panel), "After the (Remoxy) presentation, you likely now understand just how difficult it is for us to find answers to these questions…After listening to the heartbreaking stories during the open public hearing, you realize the importance of finding solutions quickly…Too many of our friends and loved ones have died from abuse, addiction…and unintended and unnecessary overdose…And pain patients are being denied access to the drugs they need…We need to listen to each other and keep their voices in our minds at all times as we try to find a path forward. We ask that you ***think outside the box*** to help us sort through these changes and find answers to these questions... Help us find the best path for (these products) and at the same time limit their availability and, hopefully, combat the misuse, addiction, and death that continues to be associated with these products…Think outside the box, please."

ALPHARMA'S PERSPECTIVE ON EMBEDA

Following a pre-IND meeting with FDA in March 2005, Alpharma conducted, under a Special Protocol Assessment (SPA) a well-controlled, parallel-group, placebo-controlled, double-blind, pivotal trial to establish the efficacy of Embeda, with exposure of ≥800 subjects to Embeda, including 100 subjects exposed daily for ≥6 months and 50 subjects exposed daily for ≥1 year. This is in addition to 12 other clinical studies: 3 efficacy/safety studies, 3 PD studies, 6 Phase I studies.

During development, the FDA advised Alpharma that a label claim for reduced abuse potential is difficult to establish. The company said it was told that development of a post-marketing program could be worthwhile to support such label claim, and the company is considering several alternative designs for epidemiologic studies to collect, trend, and analyze post-marketing data to demonstrate that Embeda represents a meaningful incremental reduction in abuse potential.

Embeda Results

Measurement	Results
Mean steady state C_{max}	Morphine was 7% greater than Kadian
Mean T_{max}	4.3 hours vs. 4.9 for Kadian
Log AUC_{0-12}	0.94-1.21, so bioequivalent to Kadian

Alpharma has not studied Embeda in children but is planning such a study.

Dr. Joseph Stauffer, chief medical officer and senior vice president of Alpharma as well as an anesthesiologist at Johns Hopkins University, said Embeda responds to the demand for a safer opioid. He cited a Centers for Disease Control (CDC) request earlier this year: "Drug manufacturers should modify opioid painkillers so that it is more difficult to tamper with and/or combine them with agents that block the effect of the opioid if it is dissolved and injected."

Dr. Stauffer insisted:

- Embeda provides safe and effective pain relief.
- There is no clinical effect from negligible naltrexone exposure.
- Embeda is bioequivalent to Kadian.
- Embeda provides similar pain relief compared to Kadian.
- Crushing is a common abuse technique, and crushed Embeda reduces euphoria.
- Intact Embeda, exposed to multiple solvents, results in limited extraction of morphine in most cases and potential extraction of naltrexone in some solvents.

Dr. Nathaniel Katz, president of Analgesic Research and a professor at Tufts University School of Medicine and Public Health, pointed out that there are 2 deaths per day in Maryland due to prescription opioid drug overdoses, "I hope you share my sense of urgency toward making some progress, even if it is incremental, toward solving this problem."

Dr. Katz noted that tampering is common among prescription opioid abusers and among addicted pain patients, "Many extended-release morphine abusers tamper with their drugs, and ~20% of patients chew their medication before they swallow it. Does tampering have consequences? Yes."

According to Dr. Katz, investigators in Kentucky found the route of ingestion changed over time from oral to snorting to injection, "Therefore, it is possible that opioid formulations that cannot be easily altered to change their route of administration might change this trajectory…A few things are clear: Patients with pain can swallow an excess dose or crush the medication and then swallow it. Non-patients crush and snort or crush and inject."

William Vincek PhD, senior vice president for research and development and regulatory affairs at Alpharma, explained the objectives of Alpharma's development program. He cited what he called "unique features" of Embeda:

- All pellets are identical.
- Each individual identical pellet contains morphine with sequestered naltrexone.
- The number of pellets determines the dosage strength.
- When Embeda is crushed, the morphine and naltrexone are quickly released, while the intact pill releases slowly over 24 hours. The morphine and naltrexone are released proportionally when Embeda is crushed.
- Potential abuse of Embeda was studied with both intact pellets and by solubilizing crushed pellets.

Dr. Vincek said a double-blind, crossover, placebo-controlled trial in 19 opioid-experienced, non-dependent subjects established the naltrexone PK and used a "drug liking" measure to select the formulation ratio in Embeda. The following extraction test chart became a big topic of conversation by the panel.

Results of Extraction Tests of Embeda Intact Pellets

Solvent	Selective extraction of morphine	Potential to minimize abuse	
		Oral	IV
1	27%-81% between 8-24 hours	Yes	Yes
2	~10% in high concentration with quantifiable naltrexone	Yes	No
3	~100% in low concentration with quantifiable naltrexone	No	Yes
4	8%-33% between 6-24 hours	Yes	Yes
5	19%-52% between 6-24 hours	Yes	Yes
6	49%-100% between 4-24 hours with naltrexone observed at 8 hours	Yes	Yes
7	4%-100% between 15 minutes to 3 hours with similar extraction of naltrexone	Yes	Yes

Dr. Donald Manning, vice president of clinical research and development at Alpharma, described the Embeda clinical program. He said the company has shown Embeda has:

- Bioequivalence to Kadian.
- Pain relief equivalent to Kadian.
- Uncompromised efficacy and safety.
- A blunting effect on euphoria when crushed.

Efficacy and Safety Results with Embeda

Measurement	Embeda	Placebo	p-value
Study 301			
Primary endpoint: Change in BPI average pain score	- 0.2	+ 0.3	0.045
No opioid withdrawal syndrome	0.6%	2%	---
Study 301: ***Secondary endpoints***			
BPI worst pain	+ 0.3	+ 0.9	0.003
BPI least pain	+ 0.3	+ 0.8	0.036
BPI current pain	+ 0.4	+ 0.9	0.026
In-clinic BPI average pain	+ 0.7	+ 1.5	0.002
WOMAC Composite	+ 1.6	+ 5.8	0.031
Safety in Study 301 and Study 302			
	Embeda	**Kadian**	---
Constipation	24% - 31%	46%	---
Nausea	17% - 21%	39%	---
Somnolence	6% - 14%	28%	---
Vomiting	7% - 9%	23%	---
Dizziness	3% - 9%	19%	---
Dry mouth	3% - 6%	15%	---
Pruritis	5% - 7%	14%	---
Headache	6% - 8%	13%	---

Sandra Comer PhD, a neurobiologist in the Department of Psychiatry at Columbia University, reviewed the abuse liability studies with Embeda – Study 205 (oral) and Study 106 (IV). The amount of naltrexone liberated from crushed Embeda is sufficient to reduced morphine-induced euphoria either by the oral or the IV route, she said, adding, "Based on my experience, ratings of 'drug liking' tend to be correlated with drug-taking behavior…This suggests that drug abuse potential of ALO-01 (Embeda), when crushed, is much less than ER morphine." However, she admitted that there are wide variations in subject response, with 12.5% of subjects not having reduced drug liking with crushed Embeda and 31% of subjects not having reduced euphoria with crushed Embeda vs. immediate-release morphine.

Study 106 was a single-center, double-blind, single-dose, randomized, placebo-controlled, three-way crossover study in 28 opioid-experienced, non-dependent subjects. The study found "feeling high" was three times greater in the morphine-alone subjects vs. Embeda, and the euphoria was greater in morphine-alone subjects vs. Embeda.

Dr. Stauffer then reviewed the company's planned risk management program/REMS. He said, "We implemented a Kadian REMS a year ago, and we are committed to a REMS for Embeda. A REMS is a prudent step." He described how Alpharma responded to an "outbreak" of abuse in Tennessee, and emphasized how the company plans to vigilantly monitor for abuse and take quick and appropriate intervention when a problem is found. One tool will be NAVIPPRO; another is a planned web-based National Opioid Safety Course. And the company plans a medication guide, a patient opioid agreement, a patient screening tool, a Physician's Guide for Response Opioid Prescribing, a Practical Guide for Prescribing, etc. He added, "An additional concern is that patients and physicians may adopt a false sense of security with Embeda…We have a plan for prevention, detection, and intervention to ensure appropriate prescribing."

FDA Perspective on Embeda

Srikanth Nallani PhD, senior clinical pharmacologist in the FDA's Office of Clinical Pharmacology, CDER, indicated the FDA has several questions about Embeda including:

- The FDA believes it is not safe to administer crushed Embeda by IV, though Alpharma has animal studies underway to address this.
- Abuse studies did not address situations where morphine alone is extracted from Embeda.
- There is high variability in the reduction of maximum "drug-liking" response. None of the tested subjects experienced complete decrease in drug-liking when consuming crushed Embeda.
- Are there adequate data to claim abuse deterrence via crushing and oral consumption?
- Studies were not done with respect to abuse by snorting the crushed product or chewing and swallowing Embeda.
- Is adequate naltrexone released and absorbed via the nasal route/chewing to counter the effects of morphine?

FDA's Perspective on Methods of Manipulation of Morphine ER Products

Manipulation method	Number of events
Methods of manipulation (n=20)	
Crush	11
Chew	3
Boiling or heating	2
Dissolve	2
Methods of administration (n=22)	
Inject	11
Oral	8
Snort	2
g-tube	1

Dr. Ellen Fields, medical team leader in the Division of Anesthesia, Analgesia, and Rheumatology Products, reviewed the history of modified-release morphine and opioid/antagonist combinations. She indicated that one combination product may have proven successful but another has not. Two

opioid-antagonist combinations – Talwin NX and Suboxone – had naloxone added to mitigate IV abuse, but Dr. Fields concluded, "There is some evidence that introduction of Talwin NX led to decreased pentazocine abuse. There has been no formal assessment of Suboxone's impact on abuse, but there have been multiple reports of IV and intranasal abuse… Naloxone does not always prevent abuse."

Dr. Fields cited a ***Baltimore Sun*** report in December 2007 which said: The Maine health department reported in August (2007) that misuse spread rapidly as more Suboxone was prescribed. Abusers of the drug "have figured out how to separate out the naloxone" to inject the buprenorphine. In Massachusetts, "A lot of people are injecting it. They're getting hooked on it."

The FDA's Governale, a pharmacist in the Division of Epidemiology, reported on outpatient drug utilization trends for extended-release morphine products. She said that in 2007:

- 5.5 million prescriptions were written for 1.2 million patients (ER and IR morphine combined).
- ER morphine products quadrupled from 1998-2007 to ~4.2 million prescriptions.
- IR morphine products (tablets, solutions, concentrate, drops) also increased from 1998-2007, from ~500,000 to ~1.3 million.
- >70% of oral solid morphine (IR and ER) were sold in retail pharmacy channels.
- Nearly 85% of oral liquid morphine products were in non-retail distribution.
- Morphine products (and fentanyl products) accounted for only 3% of dispensed prescription drugs.
- Generic morphine sulfate ER accounted for >70% of the morphine ER market.
- Kadian had 15% market share, Avinza 13%, and MS Contin 1%.
- The leading prescribers were: general practitioners (24%), anesthesiology (17%), internal medicine (16%).

Dr. Dormitzer from the FDA's Division of Epidemiology discussed morphine abuse rates in the U.S. She said abuse of controlled-release (CR) morphine has remained relatively stable over the last four years, but non-medical use of morphine IR has more than doubled.

PUBLIC WITNESSES ON EMBEDA

Several public witnesses spoke in favor of approval of Embeda, but others didn't address the drug directly, instead urging the FDA not to impose onerous risk management programs (REMS) on opioids.

➢ **Pro – Dr. Albert Ray, psychiatrist at the University of Miami, spoke on behalf of the National Pain Foundation**. He warned the FDA that over-regulation could threaten legitimate pain patients' access to pain medications, "The problems we have relate to drug diversion and abuse…Those problems create pressure to create solutions to that problem. One of the solutions tends to be political pressure to create laws and regulate medical care…That doesn't work. The unintended consequences of those laws is to deny proper access to legitimate patients…We are looking for solutions… To have more drugs available will help change the situation we are dealing with at the present time…Abuse-deterrent medications will allow practitioners and patients better access to appropriate medications…The drug czar in Florida is pushing for a drug threshold law…That cannot work. It medically limits the amount of medicine a patient can get without a special consultation. There are not enough pain doctors in the U.S. for those consultations."

➢ **REMS – Dr. Cameron Muir of the National Hospice and Palliative Care Organization**, who said he was speaking on behalf of the 4,000 hospice programs and the nearly 200 palliative care programs in the U.S., commented "Access to appropriate pain therapy is an important part of hospice care. We understand the drugs so important for hospice care are also drugs of abuse…If the FDA deems this (REMS) necessary, we urge that they proceed with care. If REMS are prescribed for some but not all opioids, the danger is prescribers will move away from those opioids with REMS and to those without REMS…So, it would seem advisable to approach REMS as a class issue, with all opioids carrying the same or similar risk…We urge the FDA to approach this issue with caution."

➢ **Pro – Micke Brown, director of advocacy for the American Pain Foundation**, asked the FDA to balance two problems: prescription drug abuse and under treatment of pain, "We must not pit them against each other. It is not either or, it is both…Development and approval of new formulations of medications that include these extended-release formulations that are less easy to adulterate (can help)…We do not oppose programs and processes…as long as the situation doesn't become so complex that it is a setup for frustration… REMS appear to hold promise, but there are potential problems…One could argue that if legitimate access is hampered, some will go to (illegal sources)…We hope the FDA decides to recruit a special work group of expert opinions and work on creating collaborative solutions."

➢ **Pro – Frederick Burgess, an anesthesiologist and past president of the American Academy of Pain Medicine**, said, "What we need are additional choices…The tamper-resistant products will be very useful in managing some of our very difficult patients."

➢ **Pro – Phyllis Zimmer, a nurse practitioner at the University of Washington and president of the Nurse Practitioner Healthcare Foundation**, said, "Don't ask us to prescribe fewer pain medications…That is not a viable option …Instead, we need more pain medication education...and a

wider array of medications so care can be individualized… And we need medications with built in mechanisms to guard against abuse."

➢ **Pro – Charles Cicchon, executive director of the National Association of Drug Diversion Investigators**, said Alpharma has been a strong supporter of his organization, adding, "We applaud Alpharma for its effort to develop an abuse-resistant medication that also provides pain relief for patients."

➢ **Pro – Lance Merrill from Dads Against Drug Dealers** said his trip was paid for by Alpharma. He told the story of the death of his 19-year-old daughter whose experiment with his painkillers started her down the path of heroin use. He said, "We are facing an epidemic, and there is a need for these opioids, but there is a huge problem…In the Middle Ages the Black Plague killed millions of people. In the 21st century we are facing a White Epidemic…We will see millions of people die because of opioid abuse…We have the power to change this…We can close the bridge between opioids and heroin… The entry level drug of today is not marijuana; it is opioids… When opioids are not available, they turn to heroin…The opportunity is there for a tamper-resistant opioid which can make pain relief available but at the same time prevent problems…It is a road we need to keep open but a bridge we need to close."

➢ **Pro – Gwen Herman, executive director of Pain Connection and a pain/fibromyalgia patient herself**, stressed how important it is not to make doctors afraid to prescribe pain medications for legitimate patients.

➢ **Pro – James Broatch, executive director of the Reflex Sympathetic Dystrophy Syndrome Association**, said, "We strongly endorse this new drug application for Embeda." He reported the findings of a recent online survey of 513 of his members which didn't exactly support that statement:

- 42% use opioids for pain.
- 49.3% of these take a sustained-release opioid.
- 87.1% would not be deterred from taking an opioid if it contained an abuse-deterrent compound.
- 44% said caregivers would be more comfortable if they were taking an opioid with an abuse-deterrent component – ***but 55% would not***.

➢ **Pro – Katherine Walker, a pharmacist at the University of Maryland School of Pharmacy**, suggested that Embeda might help patients feel more comfortable about taking an opioid, "Patients are afraid of becoming addicted or having the medication in their house…We should do all we can to protect the patient and the prescribers…If we had something to reassure them that some safeguards are in place for tamper-resistance, wouldn't that be (beneficial)?...I see an important role for this (Embeda) in preventing the high (abusers) are looking for…I think this can help engage a key portion of the diversion picture…Embeda would offer some protection against diversion by providing a barrier to tampering and would give some assurance to providers. Every other opioid preparation is able to be tampered with easily, so they are all valuable to abusers…Embeda offers us some hope in this area."

➢ **Pro – Lennie Duensing, executive director of the American Academy of Pain Management**, spoke at the Remoxy panel and again at the Embeda panel. She said many clinicians, out of fear, are no longer prescribing opioids even when they know they would be an appropriate treatment, "We need the widest variety of pain medications available to physicians, including abuse-deterrent opioids. Abuse-resistant opioids may increase the likelihood that physicians will prescribe them for patients who need them." She added, "We are concerned REMS will have a multitude of requirements on patients, pharmacists, and providers that are so complex, costly, and time-consuming that they, in and of themselves, will be a barrier to optimal pain management."

PANEL DISCUSSION OF FDA QUESTIONS ON EMBEDA

QUESTION 1a. Discuss the adequacy of the tools we have to assess the impact of a novel opioid formulation on abuse, misuse, and diversion of Embeda in the community.

Most of the discussion on this question focused on risk management plans (REMS), surveillance, and labeling. One suggestion the panel discussed at length was development of guidelines in conjunction with several of the medical societies. Some panel members thought this would be a very good idea, but in the end most seemed to agree that this would do little to achieve the FDA's goals.

General comments included:

- *Daniel Zelterman PhD, a statistician from Yale University School of Medicine:* "The methamphetamine crowd is pretty resourceful…They have developed labs in basements and warehouses. When we talk of abuse and how easily you can extract opium from the medication, the comparison shouldn't be if you can crush or dissolve it in boiling water, etc…You should always compare how easily an opioid can be extracted vs. a methamphetamine lab. That should be the comparison."
- *Dr. Kerns, a pain management specialist from Yale:* "I agree on developing an evidence base…and I would develop some strategies…for two populations that deserve special attention: those known to be vulnerable on under treatment for pain (women, minorities, HIV/AIDS patients) and those…with a history of substance abuse."
- *Public Citizen's Dr. Wolfe:* "I think, short of some hard-to-imagine miracle, any tamper- or abuse-resistant product, if anything gets approved, it will be closer to what is out there right now…There are certainly people who have – at a local or national level – done evaluations of what is going on now, and if those evaluations are carried forward and fine-tuned, they will have greater

impact than every incremental addition of a novel formulation…People are over-estimating the magic of the novel formulation."

- *NIDA's Dr. Denisco:* "Many of the epidemiology tools are funded by SAMHSA and NIDA, and I don't know with the current economic situation that exists that we can count necessarily on being assured these will continue to exist…If there are modifications or changes in these surveillance systems, backups will have to be developed to adequately assess the impact of these new medications."
- *Patient advocate Yesenko:* "I find it amazing there has never been a National Opioid Safety Course in place." (NOTE: *Alpharma is proposing one in conjunction with Embeda approval*.)
- *Lesar, a pharmacist:* "I am very much stuck by the differences in the data yesterday (Remoxy) and today (Embeda)." He said there were positives at both the Remoxy and the Embeda panels, but in different ways that did not overlap very much, "I'd like to see some of the (Remoxy) tests done on this (Embeda) product, and vice versa…There are different tools that need to be applied to all drugs…I was struck by the differences in the two days of presentations."

Comments on REMS included:

- *Dr. Lorenz, an internal medicine specialist:* "(An) issue that is worth reiterating is thinking about aspects of the REMS strategies that focus on post-distribution supply – and monitoring and limiting supply in appropriate and non-invasive ways – like pricing, even though that doesn't fall under your authority." He suggested using captured populations where the numerator and denominator can be linked.
- *Dr. Nancy Nussmeier, an anesthesiologist from the State University of New York:* "I found it disconcerting that there were no studies of any REMS program…I would agree with calls for consistency in REMS programs of the opioid class."
- *CDC's Dr. Paulozzi:* "The REMS today was more show than substance, and this is kind of annoying to be shown pictures of high school students in computer class implying there is some high tech response center." He suggested that manufacturers put a marker chemical in opioids that could be detected by toxicology.
- *Acting panel chair Dr. Kirsch, an anesthesiologist:* "I'm struck by the comments…on the need for commonality in REMS….And I echo the request for commonality in assessing the important tests to see if something is abuse-resistance or tamper-proof."
- *Dr. Kramer:* "A component of any REMS has to be an evaluation piece in terms of impact. There shouldn't be any REMS without evaluation…I think the FDA is… positioned to write integrated guidelines for practicing clinicians…and I'm even imagining collaboration with some professional societies to come up with a description of alternative treatment options and pros and cons. I worry that the way it is now, you will see all these packets of (REMS) information…There is no way to read it all, and I have skepticism about the objectivity of it all."
- *Dr. Wolfe:* "A gorilla in the room is advertising and promotion…REMS is a new statutory authority to get companies to put in programs…but it is the company, not the doctor that is being regulated. Doctors, in too many ways are being regulated by advertising…Family practitioners, general practitioners, internists, etc., are heavily buffeted by advertising and promotion. This whole REMS idea…still does not put FDA in the position of regulating doctor behavior…In the infancy of REMS, we have to focus heavily on advertising and promotion… Any company that wants to develop a product that is novel and has significant benefit – which I hope they will – will spend a huge amount of money advertising and promoting it. They will go as far as they can…to sell as much of this drug as they can. This is a huge dilemma."
- *FDA's Dr. Rappaport:* "This is the infancy of REMS. The law was only passed last year, and it is still being sorted through. We are here to get more information from you, companies, and open public speakers, and sort through what will be in the REMS if we are going to have them for these products."
- *Susan Krivacic, a patient representative from Austin TX:* "I've seen a lot of passive tools in REMS, but they are good tools. I think we need more active tools."

Comments on guidelines included:

- *Dr. Rosenberg, an anesthesiologist:* "There are a wide variety of pain guidelines that talk about how to administer chronic opioid therapy…And they are remarkably similar…But, in fact, most of the problem patients we're talking about here are those who fall in the gray areas of the guidelines or in areas the doctors decide that in the interest of wanting to help the patient, they will choose to bend the rules a little bit…And that will require a lot of expertise and be very difficult for many primary care providers…A common education package is easy. It's been done. Pick three (medical) societies and put guidelines together, and they would vary (very little)."
- *Dr. Sorin Brull, an anesthesiologist from the Mayo Clinic:* "We all fear education is commercially-driven… As long as we have specialty societies buy in, and they get recognized as guidelines for practice, they will become really universal…And the same guidelines (would) pertain to management of chronic pain…The document can be an open document, can be one document to which every specialty society subscribes and which forms into guidelines."

- *FDA's Dr. Hertz:* "Guidelines exist. What do we do to get those operationalized?"
- *FDA's Dr. Rappaport:* "We are all on the same page here …We agree there should be a standard set of tools on how to assess the abusability of a product and a standard set of tools to look at how whatever those features are we do approve for a product actually impact the community …So, the question is what should the components of those tools be? What should the pieces be that go into best practices for assessing abusability and surveying abusability?...We've heard a fair amount of useful information in that regard…Keep in mind that what you are talking about is every physician in primary practice prescribing these medications, and it is not a matter of guidelines. It is a matter of enforcing that they attend to them and follow them. How do we enforce (guidelines)? That is the problem."
- *NIDA's Dr. Denisco:* "The problem with guidelines is they are not evidence-based. They are consensus expert-opinion guidelines. They don't carry the full weight of evidence. They are the best we have right now. There are studies underway that we should see in a major publication in the next couple of years…What I've been privileged to see so far will go against the common knowledge that we all hold in the guidelines…So, I think we will see a radical change in our thinking on this topic based on the evidence and not expert opinion. And without that evidence base, you won't have the authority that it is expected, and it won't go into wide medical practice."
- *Dr. Kramer:* "If you had a standard that everything in the guidelines should be evidence-based, we are sorely away from that just because of huge gaps in evidence…The funding mechanisms to answer all the questions we have are just not there…As the level of uncertainty increases, the guidelines get longer and longer…You take family practice doctors, and they won't read the (long) guidelines. So, if you want family practice doctors and people on the front lines to use guidelines, they have to be condensed to the core message that is most important… Doctors who prescribe narcotics have to have their DEA number renewed…So, there are ways to get people to do things."
- *An industry representative, D. Bruce Burlington, a pharmaceutical consultant:* "I think it is important that we not focus on trying to force physician adherence to guidelines…It is the FDA's job to regulate industry, not the practice of medicine."
- *Dr. Paulozzi:* "Chronic pain guidelines would have limited impact…because there are a lot of data dishonesty and duped physicians out there…Disciplinary action courses are ineffective if not a joke. Guidelines will not address that group…One approach has to be expanding prescription drug monitoring in states to look at individual prescribing practices to identify patterns, etc…Those (efforts) have some chance of having an impact…Forty percent of opioids recently prescribed are in emergency rooms, and a lot of that is not chronic pain. We need some acute pain guidelines, so it isn't an intern giving 30 days of percocet to someone coming in."
- *Patient advocate Krivacic:* "We talk about educating physicians, and we haven't talked about educating patients or the abusers or potential abusers or the young people out there being affected in large numbers…I'm not sure young people are really aware of the dire consequences of these drugs. Perhaps something should be put on Yahoo or MySpace."

QUESTION 1b. Discuss whether or not the available data suggest that this formulation will be less susceptible to abuse and misuse.

An informal poll of the panel indicated that **about two-thirds believe Embeda is at least slightly less susceptible to abuse and misuse** than other extended-release morphines.

- *Dr. Nussmeier:* "My conclusion is that it is a small advance but an advance. I have a lot of concerns about issues like high variability among individuals in drug liking. We didn't hear anything on snorting or chewing this formulation. We didn't really get an answer on heating or cooking it on a spoon and what would happen. We know there are problem issues with the safety of IV injection…It would be really laudable if the company had trials in people with acknowledged addiction, but in the absence of that, it is probably at least a small advance."
- *Dr. Lorenz:* "I would reiterate that…We would like standardized (language) that reflects abuse across all products."
- *Industry rep Burlington:* "There is no doubt any formulation that can be absorbed by the human body can be defeated by a chemist…I also have no doubt that sooner or later we will see recipes on the internet for doing this… However, I do think this is an advance in the sense that it does make it more difficult…I don't think it is clear this product will be less abusable…If this is approved, there would have to be some comment about the advantage…I would argue strongly that the disadvantage of this – the widespread use of something perceived as more tamper-resistant – would outweigh any advantage, however small."
- *Patient advocate Yesenko:* "My concern is the potential to minimize abuse…With (one of the) solvents, there was no potential to minimize abuse in IV, and in (another), there was no potential to minimize abuse with oral administration…That is why we are here…Is this formulation less susceptible to abuse and misuse? I think we have our answer. I do anyway."
- *Dr. Kramer:* "It seems to me the sponsor has shown that with oral administration there is some advantage with this formulation…My concern is that we have not demonstrated it prevents problems with IV administration. And

I'm concerned there was individual patient variability… On average, it does look better, and it is an advance…It is not right to say it doesn't have some advantage over Kadian."

- *Dr. Paulozzi:* "I think one of the issues with figuring how much benefit there will be is the quality of the data and the route of exposure…Most of the mechanisms (discussed) have to do with crushing…What percent of exposures are oral? I don't think we have very good information on that. Some of the data…show different rates of exposure, but it is prevalence data…rather than incidence data."
- *Dr. Denisco:* "I don't think this does offer an advantage."
- *Dr. Rosenberg:* "I would say this formulation is an incremental improvement…and I would like us to consider the volume of morphine abuse is much smaller."
- *Dr. Zuppa, a pediatric critical care specialist:* "The data presented indicate, from what was shown, that (Embeda) is less susceptible."
- *Dr. de Wit:* "The drug abusing population will find a way to get the morphine out…The question is how long it will take…On the face of it, (Embeda) has less likelihood of abuse…but there is a chance a small group of abusers will defeat it, and how much of that can we tolerate?"
- *Dr. Kerns:* "It is an incremental benefit, but it is marginal, and I agree that it is a methadone, not an oxycodone product, so that lowers my concern and makes me more supportive."
- *Panel chair Dr. Kirsch:* "I think it is less susceptible… but it doesn't address IV (abuse)."
- *Dr. Brull:* "I do think there is an incremental benefit. Having a Norton anti-virus program will not ensure there are no (computer) viruses, but we have to start somewhere…(Embeda) does provide an incremental improvement in decreasing the potential for abuse…I'm less concerned about the potential complications from use…I have slightly more concerns on (Remoxy's) safety…At least this product does provide an incremental benefit. It is not perfect – and none of the (computer) anti-virus programs are either."
- *Dr. Zelterman:* "My first impression is this is a very clever idea. But as the day progressed, I had the idea that it had not been developed and studied as carefully as it (should have been). We need more safety and IV use data …After you build the lock (tamper-resistance), you have to find the key (the way to defeat it)…You have to figure out that shortcut. Maybe it is easy. You have to think of that also."
- *Patient advocate Krivacic:* "I also think it is an incremental improvement."

The panel chair gave the company an opportunity to speak on concerns about how Embeda would be advertised, and an Alpharma official said, "It is important for us, as a company, to make sure that we use the right ways to sell this medication …Specifically, I'm talking about not treating unintended consequences of a false sense of security…There is no simple solution." He said the company has several studies under consideration, including:

- A randomized controlled trial vs. morphine ER comparators in higher risk patients with chronic pain.
- A randomized controlled trial vs. morphine ER comparators in the general population with chronic pain.
- An epidemiological study vs. morphine ER comparators of the rate of abuse by tampering in addiction treatment patients.
- An epidemiological study vs. morphine ER comparators of the rate of abuse by tampering in poison control center exposure.
- An observational study vs. morphine ER comparators of the rate of abuse in clinical practice.

QUESTION 2. Many of the cases of addiction, overdose, and death are associated with abuse of intact controlled-release opioid products. Embeda is formulated to release naltrexone only following physical manipulation. Discuss whether inclusion of data on the release characteristics of the naltrexone in the new formulation into the product labeling could potentially mislead prescribers or patients into thinking that this new formulation, when taken as directed, is less likely to be addictive, or unlikely to be abused or result in addiction or overdose.

- *Dr. Lorenz:* Until there are (more studies), it is important to be cautious on implementation and labeling…Labeling should reflect it is a novel formulation of a product rather than claim it is clinically effective in reducing abuse potential."
- *FDA's Dr. Rappaport:* "No one is getting a claim of reducing abuse until they have proven it."
- *Dr. Kerns:* "One unfortunate side effect of this medication being put on the market with this labeling would be further stigmatization of certain vulnerable populations… including race."
- *Dr. Kramer:* "I do think there is a concern no matter how (it is labeled)…The label probably should say something to the effect that prescribers should not consider this will avert misuse of the oral use of the preparation – something to actually indicate this won't solve your problems."

QUESTION 3. If you believe that the data suggest that this formulation of controlled-release morphine is likely to reduce its abuse and misuse, discuss whether or not any of the data should be included in the product labeling?

- *Dr. Wolfe:* "This gets down to the issue…of a false sense of security. At the level of the prescriber, would you be more inclined to prescribe it if you knew the core of naltrexone was there, and there were data to believe it reduced abuse? The problem with that is measuring two unknowns. Marginal at best is all I could say on the benefit. But in terms of risk, any lowering of the threshold to prescribe to someone to whom they wouldn't prescribe without this feature (would be a concern)…The history of oxycodone teaches us the immeasurable false sense of security was dispositive and dangerous."
- *Dr. Brull:* "I agree…Beyond that, in order for us to assess risk, my concern is what happens if (someone) overdoses on this drug. We don't have any data on large doses, and that would make me not want to prescribe it. I would want to know the effect if they overdose, knowingly or not."
- *Dr. Nussmeier:* "Definitely, the data on the naltrexone center that is related to crushing or chewing, that is good for clinicians and abusers to know."
- *Dr. Denisco:* "I would be very careful to emphasize that crushing this medication could precipitate withdrawal, which would be very unfortunate and could have serious consequences if it occurred in an elderly patient with compromised cardiac function. So, as a safety measure for this medication in terms of abuse potential, I would be very careful to make sure this stuff is ***not*** crushed for nursing home or elderly patients, whatever."

FDA REACTION TO THE PANEL DISCUSSION ON EMBEDA

FDA officials spoke with reporters after the panel meeting. Asked how what the FDA heard at the Embeda advisory committee differed from the message from the Remoxy panel, Dr. Rappaport said, "(After the Remoxy panel) I was a little concerned because I didn't feel I was getting a lot of useful information…but in thinking about it and discussing it with colleagues and hearing more (at the Embeda panel) – the conversation got deeper (at the Embeda panel) – and thinking back on what we heard from the companies and from the open public hearing speakers, I think there has been quite a bit of useful information that helps us move forward…The committee members were able to get a better broad picture of the issue by sitting and listening to two products over two days, and it allowed them to address the questions and difficult challenges in ways that actually were providing useful information on how to move forward." Dr. Rosebraugh, director of the FDA's Office of Drug Evaluation II, added, "By seeing a couple of different products, they thought more about how to handle the class instead of a single product…thought broader on how to evaluate the class of drugs…I think it was helpful for them and us both."

Although the FDA has not yet requested REMS for Cephalon's Actiq and Fentora, officials suggested that they are both likely to get a REMS in the future.

Asked about the panel's general sentiment that Embeda is an incremental improvement over Kadian, not a major improvement, Dr. Rappaport said, "I think what we heard is that many of them think an incremental change is a start, and we still need further evaluation, and we need to carefully monitor, survey, and quantitate the impact of the change…and look for any negative outcomes of this type of change. We listened to what they said and will take it into consideration."

Asked about some panel members' concern that Embeda might create a false sense of security that Embeda is tamper-proof, Dr. Rappaport said, "Someone said that one thing we should consider is outlining in the product labeling what this product can and cannot do for patients and for abusers…I thought that was a very good suggestion that we might be able to include."

Asked about the FDA's ability to restrict Embeda (or Remoxy) advertising, Dr. Rosebraugh said, "REMS does not really affect advertising, so that is not something we control." Dr. Rappaport said, "Whatever is in the label at the time of approval will be carefully monitored by the folks at the Agency who deal with advertising and promotion to make sure they are not misleading people in ways other companies have done in the past." Dr. Rosebraugh added, "That is why you spend a lot of time trying to figure out what goes in the label …The advertising has to have a fair balance."

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