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by D. Woods and Lynne Peterson

SUMMARY

Progress on a REMS for long-acting opioids is moving slowly, and implementation is not likely until 2010 or even 2011. ♦ An FDA advisory committee meeting on the REMS is expected in the future. ♦ The FDA is not ruling out the possibility of pulling long-acting opioids from the market, but the Agency really considers that a last resort and does not expect that to happen. ♦ A consortium of 25 pharmas is working on a medication guide, a communication plan, and other elements to assure safe use of opioids, including a patient-physician agreement form, an implementation system, a timetable for submission of assessments, and cooperation with the DEA and state licensing bodies. ♦ Among the suggestions given to the FDA were: a pilot program, tracking systems, multidisciplinary approach, education, and patient contracts. ♦ Two generic manufacturers asked for a separate REMS for methadone products, but that appears unlikely. ♦ Patients are worried the REMS will restrict their access to opioids, and families who have lost loved ones charged that the FDA is not acting fast enough to restrict dangerous drugs. ♦ FDA officials insisted that the REMS is not holding up decisions on pending abuse-resistant opioids. ♦ Unapproved narcotics are being removed from the market, but the companies can submit ANDAs to get them approved. The question is: Will they?

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FDA Restrictions on Opioids

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The FDA has begun a long and complex process to address problems with opioids. It has given some unapproved narcotics a timetable to be off the market, and it is preparing a new risk evaluation and mitigating strategy (REMS) for extended-release opioids. This REMS will cover generic as well as brand name products that are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. However, another REMS is expected for immediate-release (IR) opioids in the future.

In February 2009, the FDA said that it was taking steps to force 16 manufacturers of two dozen opioids to comply with the new REMS that is being written. In addition, any new long-acting opioids would have to conform to the new REMS. The FDA then began meeting with stakeholders (e.g., manufacturers and representatives from medical societies). It held a two-day public hearing in May to collect comments and suggestions for the long-acting opioid REMS.

At that hearing, nearly 80 speakers offered their perspectives and/or advice. The FDA is not finished collecting public comment; people can still submit written positions, comments, and suggestions until June 30, 2009, as part of the federal docket. Dr. Douglas Throckmorton, deputy director of the FDA's Center for Drug Evaluation and Research (CDER), said that the FDA may schedule a third public hearing, and the topic is likely to be taken to an FDA advisory committee as well.

A REMS for Long-Acting Opioids

According to Dr. Throckmorton, the REMS for long-acting opioids will reduce the risks of misuse and abuse and help achieve a balance between risks and benefits for those drugs. He said that under the Food and Drug Administration Amendments Act of 2007 (FDAAA), "FDA intends to use this new authority to mitigate the risks of certain opioid drugs…The question is how to minimize the burden on the healthcare community and patients while achieving the objectives – making sure that the benefits outweigh the risks." He said the meeting also is aimed at determining how the FDA should evaluate the REMS to determine whether or not it is achieving the intended goals and what metrics sponsors should use to assess risks.

The FDA is trying to balance the risks and benefits of long-acting opioids. Dr. John Jenkins, director of the FDA's Office of New Drugs, CDER, said, "The FDA recognizes the value of opioid analgesics…We also recognize that the misuse and abuse of opioids…has continued to grow despite the efforts of law enforcement

officials…It is essential that we try to rein in this problem. The FDA recognizes how complex the challenges of establishing a system is."

FDA officials said that a REMS for opioids would likely include elements to assure safe use and to ensure that prescribers, dispensers, and patients are aware of and understand the risk and how these products should be used. Dr. Jenkins said one critical aspect of the REMS will be the metrics.

The FDA discussion questions were:

1. **What type of education should be provided to prescribers**, and how should this certification be administered [e.g., through state medical boards, Drug Enforcement Administration (DEA), other federal or state systems, or privately through a contractor established to administer the REMS]?
2. **What type of education should be provided to pharmacists** and others who dispense/administer, and how should this certification be administered (e.g., through state Boards of Pharmacy, DEA, other federal or state systems, or privately through a contractor established to administer the REMS)?
3. Are **other REMS elements** necessary to support the safe use of approved opioids?
4. **What education should be provided to patients**, and should the system be designed to ensure such education is provided?
5. **How restrictive a system** should be designed? Is an iPledge program/registry (as for Accutane) necessary for opioids? Given patient/healthcare system burdens and the number of healthcare professionals/patients involved, how would such a system be implemented?
6. **Should the REMS include controls on distributors** who distribute products to pharmacies/others? What controls are necessary, and how can they be efficiently provided without being unduly burdensome on the healthcare system?
7. FDAAA requires that innovator and generic sponsors use a single, shared system to provide a REMS with elements to assure safe use. **What obstacles need to be addressed** before such a system could be developed?
8. **What existing systems** (e.g., in pharmacies) already exist that could be used to implement a REMS?
9. **What metrics should be used to assess the success** of the REMS?

Members of the panel were all FDA officials:

- Dr. John Jenkins, director of the Office of New Drugs, CDER.
- Dr. Douglas Throckmorton, deputy director, CDER.
- Jane Axelrad, associate director for policy, CDER.
- Terry Toigo, director of the Office of Special Health Issues, Office of the Commissioner.
- Dr. Gerald Dal Pan, director of the Office of Surveillance and Epidemiology, CDER.
- Dr. Bob Rappaport, director of the Division of Anesthesia, Analgesia, and Rheumatology Products, Office of Drug Evaluation II, CDER.
- Dr. Sharon Hertz, deputy director of the Division of Anesthesia, Analgesia, and Rheumatology Products, Office of Drug Evaluation II, CDER.

Marketed Products to be Affected by FDA REMS

Generic name	Marketed name	Manufacturer
Brand drugs		
Fentanyl	Duragesic extended-release transdermal system	Johnson & Johnson/Ortho McNeil Janssen
Hydromorphone	Palladone extended-release capsules *	Purdue Pharma
Methadone	Dolophine tablets	Roxane Laboratories
Morphine	Avinza extended-release capsules	King Pharmaceuticals
Morphine	Kadian extended-release capsules	Actavis
Morphine	MS Contin extended-release tablets	Purdue Pharma
Morphine	Oramorph extended-release tablets	Xanodyne Pharmaceuticals
Oxycodone	OxyContin extended-release tablets	Purdue Pharma
Oxymorphone	Opana extended-release tablets	Endo Pharmaceuticals
Generic drugs		
Fentanyl	Fentanyl extended-release transdermal system	Actavis
Fentanyl	Fentanyl extended-release transdermal system	Lavipharm
Fentanyl	Fentanyl extended-release transdermal system	Mylan Technologies
Fentanyl	Fentanyl extended-release transdermal system	Teva Pharmaceutical Industries
Fentanyl	Fentanyl extended-release transdermal system	Watson Pharmaceuticals
Methadone	Methadone tablets	Mallinckrodt
Methadone	Methadone HCL tablets	Mallinckrodt
Methadone	Methadone HCL tablets	Novartis/Sandoz
Morphine	Morphine sulfate extended-release tablets	Endo Pharmaceuticals
Morphine	Morphine sulfate extended-release tablets	KV Pharmaceuticals
Morphine	Morphine sulfate extended-release tablets	Mallinckrodt
Morphine	Morphine sulfate extended-release tablets	Watson Pharmaceuticals
Oxycodone	Oxycodone extended-release tablets	Mallinckrodt
Oxycodone	Oxycodone extended-release tablets **	Impax Labs
Oxycodone	Oxycodone extended-release tablets **	Teva Pharmaceutical Industries

*** No longer marketed, but still approved** **** Discontinued**

THE FDA PERSPECTIVE ON THE REMS

After the two-day hearing, the FDA's Dr. Jenkins noted that speakers provided a broad range of perspectives – passion, concern, legitimate issues.

- "Pain patients talked about the value of these drugs, allowing them to go on with their lives, but we heard from pain patients who described adverse events, and non-patient users suffered tragic consequences.
- "We heard a range on the spectrum about the benefits and risks of the products.
- "There are serious risks with these products that we need to do a better job of managing.
- "We heard a lot from the pharmacy community and their concerns how the ruling might impact pharmacy.
- "We heard a lot of comments about a pilot program or a REMS program to make sure we get it right – but we also heard comments that we should do something quickly but make sure we do it right before we do it.
- "System managers told us how the existing computerized systems for claims management might be leveraged to implement and verify participation in the REMS program and link those together, including some calls for using the existing DEA registration program as the foundation for those types of systems."

Dr. Jenkins summarized the meeting, saying that a wide range of views were given over the two days, "I think a common thread that we heard was that there was agreement that we have to have a call to action. We need to address a continuing growing problem of use, misuse, diversion, and inappropriate prescribing of opioid medications in this country. This is not a new problem. Ever since some farmer learned that you could open a poppy seed and get high…this has been a struggle for humankind. We are in a dilemma in that opioids are extremely effective drugs for treating pain. They are also extremely dangerous drugs, and the range between the effective and extremely dangerous is not very wide. So, we have a very difficult job of managing them for patients who legitimately need them…and avoiding deaths or serious adverse reactions in legitimate patients and in off-patient use. It's a very complex problem. It's a societal problem, a behavior problem, a criminal justice problem, and a healthcare system problem that we all agree we need to be working to address…We can agree that the goal for any REMS program, while probably not attainable, is that there should be no serious adverse effects and no deaths in legitimate pain patients with these drugs and the same for non-patients. They should not experience serious adverse reactions and deaths. It's probably not a realistic goal, but the goal would be to avoid any of those problems."

Where does the FDA go from here? Dr. Jenkins said, "As far as the FDA pathway, after (this two-day panel), we have to go back and digest the comments and the docket comments (open until the end of June 2009), so there will be time for people to submit (additional comments). It will be part of the FDA's job to come up with a proposal for a path forward. This is an extremely complex undertaking for the FDA, and it's important that we get a program that works and is workable to achieve the goals…maintaining access to patients who legitimately need them while making a serious effort to get to what everyone would agree is a goal that there would be no deaths related to the use of these products. That is a lofty goal, maybe not achievable in the short-run…It is entirely possible that once we form a path forward, we may seek additional public comment…It's likely we will need to seek some additional public comment before we describe to the manufacturers what we are going to require. That may take an advisory committee meeting, (where) we can propose specific questions – maybe even various options – to get input on what is the next step forward. There will be a need for some time to put this together and move forward, but we understand the urgency."

Commenting on the role of industry in creating and overseeing and implementing a REMS program, Dr. Jenkins said, "We heard some argue that industry should not be involved. The reality is that we regulate industry. The people who hold the applications are the people we have the authority to require to develop and implement a REMS program. We will be overseeing the program, and they will be required to actually make that program a reality. We will be monitoring the program and reassessing any need for changes, so there may be some who still feel uncomfortable that it's a program being developed and managed and implemented through the sponsors. That's the reality of the authority Congress gave us, but the Agency has a significant role in deciding what the REMS will be."

Dr. Jenkins said that the REMS process will take time, but he said the FDA will be working hard on it. "(It) doesn't mean that we won't be looking for short-term solutions that we can be implementing as we work through the REMS. There has to be balance between great caution and deliberation and a call to action."

FDA officials spoke with reporters after the public hearing. Following are the key questions and answers.

Why are you only looking at long-acting opioids for this REMS?

Dr. John Jenkins, director of the FDA's Office of New Drugs, CDER, said, "When we were looking at the need for a REMS for opioids, we focused on long-acting and sustained-release (formulations) because that's where we were seeing a lot of problems related to adverse events and deaths. These products have pharmacologic properties that make them long-acting. You can get into problems by dosing too frequently, or the high concentrations of the active ingredient and preparation can be defeated and lead to dose-dumping of very large doses. We heard (in the public hearing that some people believe) we should expand the program to cover all the opioid formulations, and that's something that we will think about, keeping in mind that we have to meet state requirements for when a

REMS program is warranted and can be invoked. We have to go back and reconsider whether to stay with long-acting (or all opioids)."

What is the outlook for abuse-resistant drugs that are in the pipeline or under consideration now? Are you delaying them as you wait for a REMS?

Dr. Jenkins: "We've had to work through the implications of our desire for a class-related REMS for the sustained-release and long-acting opioids and the impact on products in the pipeline. **We don't think the need for a class REMS stands in the way of approval of additional members of the class**. We can't speak about the products. We fully support the concept of new products that are less tamper prone. We would like to see products that can address some of the issues about crushing or dissolving them in alcohol or whatever – to address some aspect of the problem. We recognize that this is only a part of the problem, the abuse of the formulations – you get a rush with dose-dumping. There are other issues even when (opioids are) used according to directions. If you get an 80 mg OxyContin tablet, and you're not opioid-resistant, that can lead to serious, potentially fatal reactions. We welcome the (new) formulations. We have the challenge of understanding how to be certain they are tamper-resistant or abuse-deterrent. We are obviously reluctant to give a claim before data that demonstrate they have those properties. In a competitive environment, if you have a claim (that something is) tamper-resistant, we want to be able to see if it is supported with data."

Dr. Bob Rappaport, director of the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products, Office of Drug Evaluation II, CDER: "I would like to remind everyone that we've given each application that has come in a priority review. We've taken them to the advisory committee, and **the transcripts make it very clear where the flaws in the science were with some of those applications. With others, they may have been better, and we are doing our utmost to make sure that those products get onto the market as soon as possible**."

Dr. Jenkins: "One other aspect that we shouldn't lose sight of is that **while we heard some people (saying that we should) expedite approval, there is an equally loud contingent saying that we shouldn't approve any new products in this class. So, we've dealt with issues – like do we need to wait until class REMS to be in place before approval – but we (still) have to work through the individual applications themselves**."

Would serial numbers on pills or a patient-physician contract help?

Dr. Jenkins: "The patient-physician agreement we heard is common practice in some pain communities. The intent of the agreement is to make sure that the patient understands the benefits and risks – how to use (the drug) correctly, store it correctly to avoid it falling in hands of family members or being diverted to street drug use. One proposal we put out was about putting this into a REMS program. We also heard comments that a contract alone is not enough because signing a piece of paper doesn't mean that you understand all the details in that contract. So, it has to be more than just having the contract. It has to be patient education, physician education – the interface that they are having discussions around the contents of the contract and not just signing a piece of paper."

Dr. Rappaport: "There have been numerous proposals for different mechanisms of tracking these products as a means to look for diversion, so it's primarily a problem that would fall under the authority of the DEA. Diversion falls under their authority. However, it is important, and it would be useful information for us as well, because we do use diversion as a signal of abuse, and we see that products can be more easily tracked, and when they are diverted, and located in the community, it would help us looking to see if we can help intervene with a drug problem."

Jane Axelrad, associate director for policy, CDER: "Those technologies are being looked at by other parts of the FDA for a number of different purposes – to prevent counterfeiting of drugs, with regard to supply chain integrity, and to have a pedigree under the Prescription Drug Marketing Act. There is exploration of different technologies – e.g., identification on the package or pill itself – to tell where it originated and where it's gone through the process. Those (technologies) are not something we are looking at under our authority to require a REMS. They may come about through some other processes that we're involved in at FDA."

Dr. Jenkins: "There are multiple reasons you can do those identifying procedures. One role is to track diversion, and we heard some of that today. Another role can be to track back adverse reactions so you know who the manufacturer of the drug was, were there recall issues, and if the drugs have generics. It's often hard to know if it was the innovator product or a generic product, so there's a role for these traceability systems. We haven't said it would be part of our REMS program, but there's a lot of interest for other reasons (including) the counterfeiting aspect."

What can you realistically expect to accomplish this year?

Dr. Jenkins: "We've learned from our experience with REMS in the past year that putting together a complicated REMS program is a time consuming enterprise. There needs to be time spent by the manufacturers putting together the proper program, submit it to us, and time to review, with back and forth comments and revisions. So, this is not something that can be done very quickly. But one of our goals, when we go back and regroup, is to see if there are short-term deliverables even independent of a required REMS that we can undertake to try to start having an impact now. But it is a major undertaking that will take time."

Will there be an advisory committee meeting on the opioid REMS?

Dr. Jenkins: "We're probably going to need additional public input, so it's entirely likely we will convene an advisory committee at some point once we have formulated a plan or we may have questions so that we aren't able to develop a plan until we get further input. We will likely be continuing stakeholder meetings, meeting with industry, and I'm sure there will be further public discussion."

Will there be other class-wide REMS like this?

Dr. Jenkins: "Off the record, we hope not. (*laughter*) We've seen several cases in the last few years. We've taken action on several classes of drugs – for example, antidepressants and suicidality, Cox-2 inhibitors and NSAIDs and cardiovascular problems, and recently antiepileptic drugs. There are often classes of drugs that share risks across the class, and we may have to do a class-wide REMS. Most of the time it would fall into the MedGuide-only. Opioids are an example where we're looking at communication plans and elements for safe use. I wouldn't rule it out because we will use the authority as we see safety issues. The way the law is structured, a medication guide becomes a REMS. Even class medication guide changes make that a REMS. So, if we changed the MedGuides for NSAIDs, that would make those changes a REMS."

What does the FDA want in terms of design or data on abuse-resistant opioids?

Dr. Rappaport: "We don't have any specific guidance at this time that we're developing. This is a completely novel area of drugs, so what we're doing is, as these applications come in, we're taking them to experts to try to determine what features are most important to have within the products and what level of scientific certainty we need in order to know if they might work and actually be a deterrent, so it's a work-in-progress."

Which advisory committee would be the lead if an advisory committee meeting is held?

Dr. Jenkins: "I'm sure it would have committee representation from multiple committees, and the home committee would probably be the Anesthetic and Life Support Drugs Advisory Committee, but we have a drug safety risk management committee, and there might be other members pulled in. A risk communication advisory committee, too, was created as part of FDAAA legislation, so I'm sure that it would be a multi-committee meeting."

Dr. Rappaport: "Previous advisory committees for (King's) Embeda and Remoxy were a joint meeting of Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee."

How will a class-wide REMS be implemented?

Dr. Jenkins: "Once we have developed what we think the REMS program should look like, we'll be sending letters to companies ordering them to implement the REMS plan. We made it clear that we want one class-wide plan. Each company will get a letter, but we will be expecting them to work together to have one plan that they implement collectively rather than several plans. We won't expect to take plans for OxyContin (for example) to committee. We are viewing this as a class, but our actual regulatory vehicle is through each sponsor…We heard a call for separate REMS for methadone, and we will consider the pros and cons of that, but coming into that meeting our expectation was that methadone for pain would be included in the same REMS (as the extended-release opioids). Our authority relates to the medical use of these products. There is a bridge and interface between our authority, looking at legitimate use, and the illegal activities that may occur around products, and that is why we have to partner with the DEA. We don't envision any aspect of a REMS which would have a criminal aspect embedded in it…This has to be a multifaceted effort. The FDA can't address all aspects of societal problems that go into use and misuses of products. Our focus is on the REMS authority that we have which is directed at ensuring the benefits of the drug outweigh the risks. We are not getting to the level of policing individual prescribers. However, as part of the REMS program, there may be expectations that the program is ensuring compliance."

Implications for Other Opioids in Development

FDA officials made it very clear that they are ***not*** holding up approval of other opioids while the REMS is developed. The three opioids being watched most closely are:

1. **King Pharmaceuticals/Pain Therapeutics' Remoxy XRT** (oxycodone hydrochloride controlled-release, or PTI-821).
2. **King's Embeda** (controlled-release morphine + naltrexone), obtained with the acquisition of Alpharma.
3. **King/Acura's Acurox** (oxycodone IR + niacin).

The FDA's Anesthetic and Life Support Drugs Advisory Committee and the FDA's Drug Safety and Risk Management Advisory Committee held a hearing on Remoxy and Embeda in mid-November 2008. Acurox's PDFUA date is June 30, 2009. Acurox is an immediate-release opioid, so it won't be affected by the long-acting opioid REMS, but people are watching it because it is an abuse-resistant formulation.

However, the lack of a REMS-related delay does not mean that Remoxy and Embeda will be approved. In fact, the outlook for Remoxy is not very positive, given the negative opinions of the advisory committee. The outlook for Embeda is less clear; while the class REMS is not the issue, there are other problems for this drug.

On the positive side, these are both ordinary opioids – oxycodone and morphine – which, theoretically, could get approved under 505(b)2, but an NDA was filed, obviously because King wants to market them as safer, even though it is very clear to everyone, including the company, that they will not get a label as abuse-resistant. So, efficacy is really not an issue; it is safety. Do the abuse-resistant features make Embeda a less safe drug from the FDA's standpoint? That may be the key issue.

While there are a lot of problems with OxyContin, it is the devil that people know. The FDA does not want to create a new and potentially worse problem with a new long-acting (LA) opioid. For example, if Embeda were approved, and doctors/patients perceived it as either safer or even just different (despite no off-label marketing), then doctors and patients might be less vigilant than they currently are with LA opioids, and the abuse, misuse, diversion – and deaths – might actually go up. That would make the FDA crazy, and the prospect of that has to be in their thoughts.

The FDA also is under pressure from Congress and others – and they really do feel pressured – to do something about abuse of long-acting opioids and methadone, thus the REMS process. But that process is going to take at least another year, and perhaps won't actually be implemented until 2011. To approve a new long-acting opioid without taking action on the REMS could bring criticism the agency doesn't want. It could have the appearance that the Agency is doing the opposite of what they are being asked to do. So, there is a political problem here.

There is no question that King will have to have a REMS for Embeda, and this would be in place until the class REMS is finalized. Then, the class REMS will replace that. It is likely that the FDA is looking for King to propose a REMS that is tougher than any risk management strategy currently in place. The FDA probably does not want to impose its own REMS on King because that might be perceived as a blueprint for the final class REMS. So, the burden is on King, and that may make it a waiting game. The outcome and timing are likely to depend on what King is willing to put into its REMS.

PUBLIC SPEAKERS: THE BENEFITS OF OPIOIDS

Following are four people who told stories about how opioids have benefited them, relieving their pain; one who warned that methadone recommendations are wrong; and two who cautioned that limitation on opioids would be problematic for pain patients.

John Carney, vice president for aging and end of life at the Center for Practical Bioethics, asked how restricting opioid analgesic treatment would improve care for vulnerable populations and **warned of unintended consequences** of an opioid REMS.

John Gilbert, an attorney with a Washington DC firm that represents the pharmaceutical industry, said that it might be **burdensome if the industry were to be responsible for training or education certification**, "I'm not saying that we turn to the DEA for training…or special registration…but you could have part of the application process be some requirement that practitioners have to document or respond to questions as to whether they have completed the required training or certification."

Mark Maginn, a pain advocate from northern California, told the panel that **he has benefited from opioid medicines** for many years for osteoarthritis, fibromyalgia, and other diseases. Purdue Pharma's OxyContin (oxycodone) has turned him into "a new man."

Dr. Robert Newman, director of the Baron Edmond de Rothschild Chemical Dependency Institute at Beth Israel Medical Center, said that the **FDA is recommending the wrong dose of methadone**. The FDA recommendation for methadone use to treat pain has been 80 mg per day, with no reference to tolerance or new patients. He said that (dose) is a "prescription for death" that, with FDA approval, was in all the package inserts until 2006, when the FDA modified its recommendation to 30 mg, charging, "It (FDA) did it in such a way as to be guaranteed to be overlooked by physicians." The manufacturers insert on page 15 of a 17 page insert said that the dosage recommended is up to 30 mg per day.

He asked the FDA to send a Dear Colleague letter immediately to every physician and pharmacist authorized to prescribe or dispense methadone saying that anything higher than a 30 mg dose can kill your patients.

Carolyn Noel, a pain patient and advocate, tearfully told the panel about **her injuries from a car accident** which landed her in a wheelchair for five years.

Teresa Shaffer, pain patient and advocate from West Virginia, said that she has had **chronic pain for nearly 20 years**. A fentanyl patch has allowed her to walk and to leave her wheelchair at home.

Mary Vargas, a lawyer specializing in disability discrimination and access to healthcare, told the panel about **her pain from a car accident**, "When FDA considers implementing REMS for certain…medications, the Agency is talking about the medications I take…Yet when I read the call for public comment, some of the extreme policies discussed…were based on assumptions…that left my mouth hanging open. The FDAAA requires that elements of REMS ....must not be unduly burdensome…When you consider one more agreement…one more form to sign...these 'one mores'

must be considered in the context of...scrutiny that legitimate pain patients already face…(Pain patients) face a kind of legitimized discrimination that is based on fear…The FDA is not considering implementation of REMS in my interest… Individuals living with pain can no longer stand by while concern for those who break the law trumps their right to care …The strategies being discussed are all about law enforcement and not about healthcare…We tie the hands of patients and doctors...There will always be those who use and misuse drugs."

She tearfully asked the panel whether restricting her access to medications will give meaning to parents' loss. She predicted that the panel would see photographs of dead loved ones, "For each one of those photos, there are thousands upon thousands of other stories…stories like mine – of people who do everything right and still cannot get treatment. Patients already face incredible stigma, and any education that is focused on law enforcement and not focused on the healthcare of patients and balancing their needs, in a realistic way, not just from police officers and the DEA, that's the kind of education we need. If that information is only coming from law enforcement, it's not true education, it's biased. Pain patients are treated with a great deal of suspicion, and there is a great deal of stigma."

PUBLIC SPEAKERS: THE DANGERS OF OPIOIDS

Sixteen people told heart-wrenching stories about how they became addicted to extended-release opioids, lost loved ones to those opioids, particularly OxyContin, or how serious the problem has become in the community.

Ed Bisch, founder of Oxyabusekills.com and a member of Advocates for Prescription Opioid Drug Reform, asked, "How can a drug that has caused so much death and destruction be prescribed for moderate pain? Corporate greed and slanted studies should not dictate medical policy… OxyContin is available to almost every teen in America… What exactly is controlled about it besides the price?" He said that nothing has been done to slow the **epidemic**, including the black box warning, adding, "It is time for the FDA to take your heads out of the sand and do something about it…Stop listening to the money, lies, and lobbying…and do your primary job of protecting the American people. At the very least, OxyContin has to be reclassified as relief for severe pain only."

Fred Brason, a hospice chaplain, product director of the Chronic Pain Initiative, and chair of the Substance Abuse Task Force in North Carolina, said that rates of **unintentional opioid poisoning continue to increase drastically** in his county. He said all types of patients are dying from unintentional poisoning, and most had visited with their doctor within two weeks of death. His pilot project uses naloxone as a rescue medication for people at risk.

Brason said:

- Education does not always bring about behavioral change.
- Naloxone empowers individuals to act.
  - Optimizing dosage form requires FDA involvement.
  - A REMS can only be effective if it includes tools deployed for intervention.
- Reducing supply has consequences.

He warned that the disruption of protective opioid tolerance in non-patients could lead to an increase in overdose deaths (i.e., abuse of short-release opioids or heroin). Asked by the FDA's Axelrad if REMS should cover all opioids, he answered, "For all opiates, without proper education and proper protective measures in any type of reduction, the overdose deaths will still increase. With chronic pain patients, appropriate pain management is essential."

His naloxone distribution program is just starting this summer. Brason said that the deaths occurring in his area have moved from Wilkes County to outside the county. Asked by the FDA's Dr. Throckmorton if there is a screening process for naloxone, he said that every patient watches an educational DVD and takes it home. He added that prisoners receive naloxone.

Jerry Feldman, a former hospital administrator, said that abuse is not the only risk for management with opioids, "In hospitals, patients are dying. It is a myth that opioids are safe when used according to directions. There is no known risk stratification strategy for **opioid/ventilation-related depression**. Monitoring these patients at home while sleeping is possible and effective…It is clear that the monitored use of opioids in any form in the naïve patient or patient whose tolerance is unknown is dangerous. At a minimum, the drug's labeling should say so."

Larry Golbom, a pharmacist, host of a prescription addiction radio show in Tampa FL, and sponsor of a petition to ban OxyContin, shouted to the people sitting in the back of the room, "We're not talking about pain; we're talking about an **opium epidemic**. Today is not a meeting about pain, it's a meeting about drug companies that sell anything…to make a buck…The biggest lie is that doctors are afraid to prescribe. There's no documentation that 30 million people need these opiates…Wake up America! Are we going to allow a two-bit drug company to continue to run the FDA, or is the American public finally going to run the FDA?"

Steven Hayes, director of the Novus Medical Detox Center, said that 80% of his patients are on OxyContin or have switched to heroin because it's cheaper. He said that he deals directly "with the result of the inactivity of the FDA and the result of the gross miscarriage of justice that occurred when

Purdue Pharma was allowed to stay in business." Most of the people his center treats "came in on **legal heroin – OxyContin**. In many cases it was prescribed by a medical doctor. In many cases it came in because it was so easy to get. Some patients want to bet me any amount that they can get me 400 pills in 4 hours. It is so easily available. Since we have been here today, according to the CDC (Centers for Disease Control and Prevention), four people have overdosed and died from opioids. Forty people have gone to the emergency room on an overdose since we've been sitting here talking politely about this scourge. And I hear people talking about balance. Well, I ask you: Is an additional six minutes that requires attention from a doctor worth sending somebody to the emergency room? Is an additional hour that is required to educate people and make these drugs less available worth someone's life? Every day I see people who come to me trying to get over an addiction that is caused by legal heroin. If heroin is illegal, why is OxyContin legal? And every hour somebody else dies while we all debate this issue, and we're polite. I think it's time to look at it for what it is. It's an epidemic, and each of us in this room shares a responsibility for letting it continue – the FDA because you have power to do something about it. Everyone of these kids will tell me how many of their friends died from this." He asked why Purdue Pharma is "rewarded because they were able to buy a favor. It's time for you to do what you can to stop this."

Marti Hottenstein of Helping America Reduce Methadone Deaths (HARMD), whose **son died from a methadone overdose**, said that she expects the FDA to protect Americans and not drug companies. She said that methadone has destroyed her family, and she asked why the FDA told (General Mills') Cheerios that it was deceiving the American public with its cholesterol claims, yet won't do the same to pharmaceutical companies, "You protect American people, not these pharmaceutical companies…You just hear it; we live it."

Peter Jackson of Advocates for Prescription Opioid Drug Reform, a group of parents who have lost children to opioid-related deaths, tearfully related the story of his **18-year-old daughter who died** after taking one OxyContin pill, her only encounter with the drug. He blamed Purdue Pharma for lying about the drug and said that 80% of the opioid abuse in the world is in the U.S., "It is convenient for the drug companies …to blame the people…How many more people will die before the FDA realizes that the massive over-prescribing of opioids is responsible for this epidemic? Where is the urgency? People are dying, and the FDA is doing nothing. I'm tired of coming to these meetings…and seeing no change. He said that the REMS process, while it has some useful components, will fall short of the goal of reducing abuse…We suffer our own kind of pain that you can never begin to imagine."

His suggestions:

- Withdraw OxyContin from all U.S. markets.
- Implement a moratorium on all extended-release opioids and methadone.
- Restrict extended-release opioids to treatment of severe cancer pain.
- Give a compassionate exemption for severe non-cancer pain.

Asked what elements of current REMS recommendations would be useful, he said, "Training, certification for physicians and pharmacists are useful elements, but as long as these elements are implemented and overseen by the drug companies, it's a sham. It needs federal oversight. But we need to restrict these drugs to where they are truly needed, and we need to get OxyContin off the market."

In the open public part of the program, Jackson returned to say that, with the exception of Purdue Pharma, it might be possible for an abuse-resistant drug to be approved under the compassionate use exemption proposal, "Just the label abuse-resistant will make people think that it's even safer than products that are available now. So if there were this framework, that might offer a mechanism to creatively consider some of those new products that are coming."

Dr. Douglas Kramer, a former FDA medical officer with CDER, said that he came to the meeting because he is increasingly concerned about the **FDA's inability to control the abuse/misuse of opioids**. He said, "There is nothing in the notice of the meeting that suggests that the FDA understands the underlying cause of all opiate failures – namely, the failure to determine the appropriate dose, particularly for those not yet tolerant to opioids, whether newly released prisoners or pain candidates starting a course of treatment. The FDA rarely recommends a starting dose for naïve individuals…No amount of regulation will reduce therapeutic misadventures until the FDA understands the underlying cause of all opioid overdoses. Instead of capriciously imposing a REMS, for which there is no support…the FDA should focus on actions that will improve the safety of these products when used as directed, for which the FDA has clear authority and responsibility. In particular, the FDA should immediately clarify recommended dosing regimens for these products, with a focus on accurately describing safe starting doses for opioid-naïve patients."

Dr. Kramer said that even with a label revision in 2006 for methadone, the starting dose is still substantially more aggressive than that recommended by the American Pain Society, "FDA should move immediately to correct major discrepancies between labeling of generic controlled-release opioids and innovator products. Generic products do not contain the warnings that have been added to the innovators. This is essential in a highly generic market."

The FDA's Dr. Throckmorton asked about specific generics, and Dr. Kramer said, "I emailed this concern to Bob Temple (Dr. Robert Temple, director of the FDA's Office of Medical

Policy and director of the FDA's Office of Drug Evaluation II, CDER) and Dr. Joshua Sharfstein (principal deputy commissioner, FDA), and I believe that it is a Watson generic. The label that is on the NLM (National Library of Medicine) daily medical website from 2006 is generic MS Contin (Purdue Pharma, morphine sulfate controlled release) 100 mg dose strength. I believe that it is ANDA 75656, and it doesn't contain any of the warnings that say that the 100 mg dosage is for use in opioid-tolerant patients only, and there are many other warnings that seem to be missing from that label. These changes should have been made in 2001, 2002, and 2003."

Sandra Kresser, an advocate for banning OxyContin, described how her **son overdosed on OxyContin and methadone** prescribed to him for back pain. He became addicted to the drugs and although he went through rehab programs, he couldn't shake the addiction, and doctors continued to prescribe the drugs for his pain. She then held up a poster of photos of her son during a long silence.

The FDA's Axelrad asked about Utah's attempts to limit OxyContin prescriptions. Kresser said that she is on the task force formed in 2007 to reduce unintentional overdose deaths, "While the efforts are good, they brush the surface and don't address the real reason: Why are these drugs still in the medicine cabinets and finding their ways to the streets? The guidelines are good. They are a start and may help shed more light on the problem…But I am living proof (referring to her son) that 'use as directed' doesn't work."

Leona Nuss, speaking against OxyContin, angrily told the panel that the pro-opioid speakers were sponsored by pharmaceutical organizations and dared them to return in two years, predicting that they would be in detoxification or rehabilitation centers. She said that **her child died**, "I find it ironic that 18 years later a so-called miracle drug would take his life. He died in 2003 from OxyContin. My pain will never go away…A friend was so addicted he hanged himself in his own house at 19-years-old. Six years later, I am here to plead with the FDA to do something about this killer drug. As I speak, people are dying. OxyContin's only one supposed benefit is dosing convenience. REMS is about risk and reward. Believe me, the pain and suffering that OxyContin causes is far greater than the lone supposed benefit. I thought it was the FDA's prime responsibility to protect the American people." She showed a photo of her son before he died and held up an urn of his ashes, saying, "This is my son now."

Joanne Peterson, founder and executive director of Learn to Cope, said that a patient in her little town in Massachusetts handicapped her son for life. She heads an 800-family organization and said that she has been to 10 funerals since January 2009, "Purdue Pharma was not honest about the drug, and it has been a **modern day plague**." She wants OxyContin replaced so that cancer patients and chronic pain patients can have something. She emotionally asked, "How much more proof do we need that OxyContin is a killer? I want the pain patients to have all the drugs they need, but I want the deaths to stop. I'm sorry about your pain…and I don't care if I'm never invited back to one of these meetings, and I'm sorry if you're in pain, but I'm in pain – try living my life every day."

Betts Tully, a former opioid addict, said that she was diagnosed as a chronic pain patient and given opioids, but she is really a moderate pain patient. She said that she is here on her own, not representing a pain organization, a medical organization, or a pharmaceutical organization. She said she had eight years of narcotic therapy because of **her addiction to OxyContin**, which she was given for lower back pain. She said that she suffered, "But I didn't suffer so much that I want to be part of something that is killing these people's children and loved ones. That's absurd. It's immoral. It makes me ill to think that somehow I was stupid enough to become involved …I was lied to by my doctor…and somehow the FDA supported it. I was told not to worry about addiction, even if there was a family history. I was told that less than 1% of chronic pain patients become addicted. That's not true."

Dr. Kirk Van Rooyan of Advocates for Prescription Opioid Drug Reform said that he is "not against conventional prescription of opioids, nor am I opposed to the use of extended-release opioids for patients who truly need them." He called for a **moratorium on extended-release opioid and methadone** pain prescribing.

Dr. Van Rooyan said that prescription opioids are the second most commonly abused drugs in the U.S. He said that extended-release (ER) opioids are identical to heroin (in molecular structure), "There is no objective evidence that extended-release opioids are effective in the long-term control of chronic pain. Their only proven benefit is the convenience of less frequent dosage. There is no objective justification for using ER opioids as a first-line of defense for moderate non-specific pain. There is no credible evidence that strict scrutiny by the FDA would hurt access to true severe pain patients. How does the FDA reconcile the negative risk vs. benefit for a symptom? The manufacturers (treat pain) essentially as a disease in itself, so (opioids) are used non-selectively to treat headaches, ankle sprains, and dental extractions."

He said that the FDA's REMS plan will "contribute significantly, primarily in the area of education, but it suffers from inadequacies. It maintains that the benefit of extended-release opioids exceeds the risk historically, which is not true. The REMS should be a temporary moratorium on extended-release opioid and methadone pain prescribing...It would exempt conventional opioids and would include a compassionate use exemption."

Dr. Van Rooyan said that the REMS also does not address regulatory issues, such as more thorough patient diagnostics,

increased pharmacy and patient monitoring through a national multi-agency database. He said that the area of greatest concern is that the REMS might "allow drug companies to self-design and self-regulate. It must be implemented and controlled by an impartial third party – the FDA or DEA, not the pharmaceutical industry – which has repeatedly demonstrated that its own interest rather than pubic welfare is its priority."

The FDA's Dr. Jenkins asked what he meant by moratorium, and Dr. Van Rooyan said, "Basically, it could be a combination of things, but the initial step could be to change the indications for instance at least short term to eliminate moderate pain of non-specific sources. It would require certain basic diagnostic steps, require a certain level of competency to be demonstrated by physicians who participate in a compassionate use, for instance. The moratorium would not be long, and it would not keep people who really need it from getting what they need."

Then, Dr. Jenkins asked how a moratorium could be implemented, particularly with a compassionate use exemption. Dr. Van Rooyan responded, "We're not trying to exclude the availability of prescription pain medication from people who deserve to have it. But because there has been so much abuse and a flood, particularly of OxyContin, that a moratorium would produce a breathing spell until the FDA can formulate a definitive REMS program that would include additional research, increased competency training for physicians and patients, etc."

Dr. Van Rooyan said, "The abuse potential and toxicity of conventional opioids are miniscule compared to extended-release opioids. One OxyContin can be equivalent to as many as 40 Vicodin (acetaminophen plus hydrocodone). The bottom line is that if properly implemented, a moratorium would give the FDA the time it needs and should take to protect patient safety and still come up with a program and maybe a pilot program."

Dr. Art Van Zee, an internist in a small clinic in southwestern Virginia (Stone Mountain Health Services' St. Charles Clinic in St. Charles VA), said that the **heart of the opioid problem lies in sustained-release opioids**, which:

- Are comparable in efficacy and safety to immediate-release (IR) opioids.
- Have an increased risk of addiction when abused.
- Have an increased risk of inadvertent overdose/death.
- Have been over-prescribed and are highly available.
- Are a national problem.

He noted that the REMS as proposed by the FDA:

- Would not significantly impact the availability of opioids and single-release opioids.
- Falls short of impacting the problem.
- Would not significantly change physician prescribing behavior.
- Would not have a major impact on the economics that drive the OxyContin problem now.
- Would not significantly change physician prescribing behavior with any associated continuing medical education (CME) or test related to it.

Dr. Van Zee said that he would encourage demonstrated competency for prescribing, and he supports limited use of extended-release opioids. As for methadone, he said, "It is a subset of the whole prescription opioid problem, and it needs to have special demonstrated competency for its prescribing."

He said that opioid prescriptions increased 500% from 1999 to 2004. Of unintentional drug overdose deaths in 2005, 38.2% were prescription opioids, and of those 16.2% were methadone deaths. Another study he cited showed that 70% of overdose deaths occurred within seven days of initiation of the prescription or after a change in dose, "Showing that the patient doesn't understand the medication, the doctor doesn't understand the patient or medication, or a combination of both." He suggested making methadone available to all cancer patients and available to chronic non-cancer pain patients under a compassionate use program, prescribed by physicians with special certification of competency.

Dr. Van Zee also suggested a secure and tamper-proof method for dispensing controlled drugs, such as GW Pharmaceuticals' hand-held computerized device that dispenses pills. He also suggested marketing changes, including a redefinition of acceptable and allowable marketing practices by pharmaceuticals, and changes in regulations so that Schedule II drugs could not be prescribed off-label except through a compassionate use program.

He summarized his recommendations:

- Changes in access to single-release opioids.
- Changes in access to methadone.
- Implementation of demonstrated competency.
- Opioid preparations of minimal abuse potential.
- Requirement for point-of-care devices for dispensing of controlled drugs for chronic pain.

The FDA's Axelrad asked who would determine on a patient-specific basis whether a patient would qualify for a compassionate use program, and who would administer that program. Dr. Van Zee said that the intent would be that where OxyContin might be appropriate, "High potency opioids would not be the first thing to prescribe. There should be some demonstration that medium-release opioids don't work before going on to extended-release opioids. We need to be as selective as we can."

The FDA's Dr. Jenkins said, "The thing we're struggling with is that we're talking about – expanded access programs, which are generally used for investigative drugs while the plan is being developed. When we hear about it in this area of extended-release opioid products, are you talking about access that would be restricted under an IDE investigation? Labeling? Or would someone have to say, 'Yes you qualify,' other than the prescribing physician?" Dr. Van Zee answered, "Several years ago cisipride was recalled and then made available through a compassionate use program…I think you need some kind of rational restrictions, some kind of hoops to go through, to be sure that conscientious physicians who know that this particular patient needs this drug, can justify it through some reasonable amount of paperwork."

Dr. Jenkins asked, "How many patients might qualify for such a compassionate use? Thousands, millions?" Dr. Van Zee responded, "I'm sure it's more than thousands. It would be many. There are loopholes in everything, and that could be scammed, too. It would limit availability, but it would still have an open door for patients who have heart-wrenching stories like we've heard (here). In my practice, those who would benefit from that particular sustained-release drug, it would take a little extra work to get it."

Ed Vanicky, speaking in favor of a ban on OxyContin, talked about his **wife's death from an OxyContin overdose**, "After a car accident, she was given OxyContin, but the doctor later admitted that he shouldn't have prescribed such a strong drug. My wife fell into the 6-8 hour dosing, and that allowed the drug to stay in her system enough for an overdose." He blamed Purdue Pharma for misleading patients, "They still do business with an unsuspecting American public, and they should be banned from doing business…Letting them do their own REMS program is like letting the fox guard the hen-house." He warned that every person in the room not already affected by OxyContin will be in the near future. He asked the panel to atone for its mistakes, "We're tired of coming to meetings and hearing the same old company line. The end has got to be now. No excuses, no giving in to the drug companies. It has to end right here, right now." He said that he hopes that companies working on abuse-resistant and tamper-resistant medications are successful.

A physician who works for a pharmaceutical company told FDA officials that it is **time to develop better drugs**, "It shouldn't be so easy to take a powerful drug and make it more powerful by simply crushing it." He said it will take more than the FDA – including law enforcement and the courts – to solve the problem.

The Perspective of Professional Organizations

Thirteen officials from medical societies and healthcare professional organizations told the panel their concerns with the proposed REMS, and some offered suggestions to the Agency.

American Academy of Pain Management. Lenore Duensing, executive director, said that "opioids remain one of the most effective narcotics…for millions of people…but the FDA has yet to acknowledge that **chronic pain is one of the serious health problems in the country**. More than 33 million Americans live with pain that has lasted for more than a year, and more often their pain goes unrelieved."

She asked FDA officials to answer directly whether it is true that if a satisfactory REMS is not created, extended-release opioids will be pulled from the market. Dr. Jenkins responded, "What we said is that this is a serious problem. We're seeing serious adverse events and death, and if we can't get this problem under control it ***will bring into question the continued availability of these products or limited access to these products***. We didn't make the threat that we would take these off the market. We said we had serious concerns about adverse reactions and deaths…***The ultimate restriction is non-availability of these products***."

American Chronic Pain Association. Nicole Kelly, president of the board of directors of this consumer group, said that many people with chronic pain are afraid that they will **lose access to the medications** they need. Specific fears and suggestions included:

- The proposed certification process for prescribers and pharmacists would diminish access to care.
- Any certification should be tied to the current DEA process.
- Limiting access to specific geographic locations will diminish access to care.
- Already existing stigma will increase.
- The monitoring process should not be removed from the patient-doctor relationship.
- It would be impossible to safeguard confidentiality of people if a registry is started.
- An environment of pseudo-criminalization will only further stigmatize and punish people in pain who need medication.
- A broad public education campaign is essential to address the use of unintentional misuse of opioids.

The FDA's Dr. Jenkins asked how the DEA and the FDA could share a certification program. Kelly said that she is not familiar with the licensing provisions, but maybe state medical boards could help, "Physicians and pharmacists should be educated in basic pain management. Right now, physicians in training are not getting sufficient training in that area."

American Pain Foundation. Sandy Browne, a nurse and director of communications, said that her group has **serious concerns about the REMS being considered**, "There are millions of Americans who rely on prescription opioids in order to get up each morning and face their day…The FDA must not cause harm to a substantially larger group of Americans in order to protect another group from harm." She said her group "supports public educational efforts…but will not support patient registries, which create hardships and erect new barriers to effective pain care…Do not cause more harm for those who live with pain…by impeding their ability…to have a life worth living."

Browne mentioned **the idea of a pilot REMS program**, and the FDA's Dr. Jenkins asked what that might look like. She answered, "Once your REMS decision has been made, perhaps take one or two areas where there have been known problematic issues, such as abuse and maybe two other areas, and pilot those programs first and see what type of impact is made in mitigating issues such as misuse of medications, i.e., receiving them from patient stockpiles or also looking at those issues with regard to improper medication use once the program has been established with the providers."

American Pain Society (APS). Dr. Gregory Terman of the University of Washington School of Medicine, speaking on behalf of APS, read parts of a letter from the APS board to the FDA expressing shock and sadness at the increase of opioid-related deaths over the past decade, **calling for a multi-disciplinary solution**, and warning **that unintended harm may result from a REMS**, "Opiates are only one tool in the treatment of pain. The eyes of the world will be on the U.S. when the FDA acts. The board said that there should be care in choosing REMS which are measurable and accountable, which don't interfere in the management of patients who require medication for severe pain."

Specifically, he suggested:

- REMS should cover all opioids.
- There should be no required registry, just enhancements to current prescription monitoring programs.
- REMS components should be measurable and, when necessary, easily reversible.
- Prescriber and dispenser competency concerning opioid pharmacology should be demonstrated by all who seek DEA licensure.
- REMS education should be aimed at the public as well.

The FDA's Axelrad asked if there were data that establish a baseline about the degree of current access to pain medications, "Would a baseline have to be established, since some speakers said that pain medications are under-prescribed today?" Dr. Terman answered, "There are a couple of small, multidisciplinary task forces in the APS that are looking and hopefully will have specific suggestions (by June 30, 2009) regarding competence testing and also a metrics for studying the effect of a REMS. Two issues for us are (1) effects on disparity – prescribing medications has already been shown to depend a lot on socioeconomic class, race, and some of the people in the APS have published in this area. That would give a baseline to look for problems that develop to make things even more skewed in that regard, and (2) the other major concern would be the possibility of either pharmacists or physicians opting out of prescribing opiates. Even if it were tied to DEA registration, it's possible that people would decide that they simply do not want to prescribe them. That would obviously have an impact on care."

American Pharmacists Association. Marcie Bough, a pharmacist and director of federal regulatory affairs for the American Pharmacists Association, suggested a **pilot program**. The FDA's Dr. Jenkins asked if she had any specifics, "How would we do it?" Bough answered, "We would need a broad sample of where prescriptions are being dispensed. There could be a randomized process where we could look to see who is interested in a pilot program…all intended to address glitches, much like in clinical trials." She said that she thinks there would be enough interest for such a pilot program.

Dr. Jenkins asked for advice on how to reconcile these comments demanding a moratorium with other comments that there needs to be more research or a pilot program, "which sounds like it would take a long time before we get to a REMS." Bough answered, "When we look at existing patient information tools or ways to implement risk management programs, they may work for those intended medications, but we feel there is a lack of evidence and experience in using these types of tools to mitigate use and abuse and identify a patient population that is opiate naïve or inappropriate."

The FDA's Axelrad asked about existing systems, such as the Relay system, and Bough said, "We support the concept of a standardized back-end system which can help manage the REMS…It will be very challenging for pharmacists and the healthcare system in general to manage all the components that make up a REMS. If we have a system that can be tagged onto the system processing or adjudication system back-end, so it's seamless…it would help streamline the process and help with access points for prescribers, wholesalers, pharmacists, and patients. It's a workflow issue, and it's an efficiency issue as well."

Axelrad asked for more information on what other systems similar to Relay are available and which ones work, and Bough said she would provide some information.

The FDA's Dr. Throckmorton asked about the idea of pilot programs, "The pilot is intended to make an early start – to find what works before going broadcast. In the past we talked about other mechanisms – for example, state experience – and we've asked other people to comment on state experiments that have worked well, things that we could think of as early pilots. The second piece is to look at previous REMS experiences. Are there lessons that we can learn from looking back at some of the smaller REMS programs that we have had to implement, things that might not be working as well as you think they could?" Bough answered, "We can draw on some experiences, specifically with the TOUCH program – for Biogen Idec/Elan's Tysabri (natalizumab) to monitor for progressive multifocal leukoencephalopathy (PML) – and the glitches that pharmacies and stakeholders had in getting it up and running. We are pursuing additional feedback of implementing the current REMS from our members and pharmacies in general. One of the things that I have heard from pharmacists in the last few weeks is that one success is with the challenges in place for them. The trouble is that there is benefit when the patient realizes that there is an extra step, and there is a risk for these medications, and they may not have been aware of that."

American Society for Pain Management Nursing. A representative said that nurses are the glue in the web of the healthcare system, but little was said about them during the two-day hearing. His group has a certification program for pain management, including assessment, intervention, side effects, and patient family education and counseling. He said, "An educational certification model already exists and can help you."

American Society of Clinical Oncology (ASCO). Dr. Sydney Dy of Johns Hopkins Kimmel Cancer Center, speaking on behalf of ASCO, said that ASCO is concerned that a cumbersome REMS **would deprive cancer patients** of extended-release opioids. She suggested that the FDA work with states that already have existing controls, including registries of narcotic prescriptions. She said that cancer pain is under-treated, "It is our belief that simply monitoring the number of prescription drugs moving in the system is not efficient. Development of the metrics will be extremely complex. ASCO is against a burdensome system that compromises legitimate patient access to the drugs."

An FDA official asked if there is anything unique regarding distribution of drugs in different settings, such as hospices, and Dr. Dy said that getting opioids in nursing homes is often a problem.

American Society of Consultant Pharmacists. Thomas Clark, director of clinical affairs, said that opioid REMS would **impact long-term care facilities**, which can include nursing facilities, assisted-living facilities, continuing care retirement communities, and hospice. He said that the elderly population has more adverse reactions to NSAIDs than other populations, and that opioids are often the best alternative available.

American Society of Health-System Pharmacists (ASHP). Nathan Thompson, director of Johns Hopkins Outpatient Pharmacies, spoke on behalf of ASHP, saying that FDA **should clarify why the REMS is needed**. He said that the FDA should develop pilot REMS programs and asked the FDA to exempt hospital settings, since hospitals and health systems have systems in place to mitigate the risks associated with these medications. He spoke against patient registries and patient-prescriber agreements. He added that a REMS for opioids should cover the entire class.

National Foundation for the Treatment of Pain. Dr. Joel Simon Hochman, executive director, said that current adverse event data are "unreliable and implausible" and contended that there are **no correlations between deaths and opioid drug use**, "Even if there are 8,500 opioid deaths in a year, this is a minuscule number compared to the number of medications given each year…There aren't any drug problems; there are only people problems." *This remark caused another speaker, Joanne Peterson, to storm out of the meeting.* He continued, "The idea that reducing the availability will reduce the number of deaths is nonsense. For every tragic story we've heard (here)…what we really need to do is a psychological assay: Okay, what happened with your son? And how do we compare his tragedy with the 30 million people who spend their lives wishing they were dead…The current proposal to restrict…is, I believe, a dreadful folly. The real crisis is the unavailability of medical management and pain."

Dr. Hochman said that the number of doctors treating chronic pain is decreasing due to what he called "opiophobia." Asked what the most effective education communication tool is, he said it's to establish therapeutic reliance, "I have never lost a patient to an overdose – with 4,000 patients in almost 20 years."

National Community Pharmacists Association. Ronna Hauser, PharmD, vice president of policy and regulatory affairs, urged the FDA **not to put all the burden for the REMS on pharmacists**. She said that:

- Pharmacist training should be accredited by the accreditation council for pharmacy education.
- Patient education should occur at the physician level. The FDA could provide doctors with plain language documents to give their patients.
- A nationwide system exists that provides patient education in the pharmacy.
- A patient registry is not a good idea.

- Any state- and DEA-licensed pharmacy should be eligible to dispense opioid products.
- The TOUCH program has been burdensome. Existing nationwide technologies using existing pharmacy management software systems could be used. Electronic prescribing, any registry, and technology used to document patient understanding should all be interoperable.
- A standardized REMS process that can be integrated with existing pharmacy workflow is necessary.

Dr. Hauser said, "It is not okay when a patient is in pain and in your pharmacy and you are unable to give medication because the doctor hasn't registered in a patient registry. We should not have to serve as prescription police."

The FDA's Dr. Throckmorton asked for details about the challenges of previous REMS, "You said that current training for pharmacists is sufficient. Do you have any data on the amount of information that a pharmacist has? Do they have to pass a test?" Dr. Hauser answered, "Requirements for continuing education are different in different states."

The FDA's Axelrad asked, "You mentioned a nationwide system to provide patient education and counsel in the pharmacy?" Dr. Hauser said, "There is a system that allows pharmacists to give patients therapy management services."

National Pain Foundation. Mark Rasmussen, president/CEO, said that his organization is trying to be balanced. He described an **educational initiative** for patients, healthcare providers, and dispensers, called Painsafe. His group recommends:

- FDA must clearly provide a written definition of the key problems they are trying to remedy with the new opioid REMS, and how they will define success 3-5 years in the future.
- State prescription drug monitoring programs should be expanded to all 50 states, improved to be available to prescribers and pharmacists in real time, provide for interstate linkage, and be fully funded by the federal government.
- The FDA, DEA, and other government agencies and Congress need to collaborate and determine how best to utilize existing programs, funding, and authority. DEA has a database that includes everyone who prescribes opioids. It would be crazy to set up another system.
- Key metrics:
  - The FDA should identify the key metrics needed to evaluate the success of the REMS program and then arrange for funding and other action necessary to create or standardize collection of the measures.
  - Metrics need to measure changes in both risks and benefits of the treatment of pain with opioids based on the new REMS program.
- Risk:benefit analysis.
- Facilitate dialogues to refine REMS program.

Dr. Throckmorton asked Rasmussen about which state programs are the most useful, and Rasmussen said the most successful program is in Utah. The Utah legislature earmarked $500,000 in funds for a similar approach in that state. For all states, $28 million a year would be needed.

Oncology Nursing Society. Oncology nurse Leslie Greenberg, health policy manager of the Oncology Nursing Society, recommended **piloting** the REMS first and studying what states have done.

HEALTHCARE PROFESSIONALS AND CORPORATE SPEAKERS

Representatives from 13 widely different groups also addressed the panel.

Colorado Pain Initiative. Chris Kottenstette, a physicians assistant and member of the Colorado Pain Initiative, asked the FDA to treat all providers and pain patients the same way. He said, "**Physicians should not be allowed to opt out of pain management**. All medications need to be treated similarly. Separating them would only suggest that some opioids are safer than others…People feel safe that these are prescription medications…If you allow physicians to opt out, you are going to move the burden of care and significantly burden the whole community…More than half of abusers get the opioids from friends and family. A prescription monitoring program is not going to fix that issue…because the prescriptions are coming from one physician."

He warned that excluding short-acting opioids from a REMS would only shift the abuse from extended-release opioids to immediate-release opioids, "To say that the short-acting opioids are safer and shouldn't be included in a REMS program is misleading because they can be misused just as easily."

College on Problems of Drug Dependence (CPDD). Jack Henningfield, professor of behavioral biology at Johns Hopkins University School of Medicine and vice president of research and health policy at Pinney Associates, speaking on behalf of the CPDD, said that the CPDD is the leading scientific organization looking at drug dependence. He said that implications for REMS include:

- A **class-wide REMS will have implications for drugs in the pipeline**, not just the approved drugs receiving current focus.
- REMS could either facilitate or discourage new drug and dosage form development (e.g., new molecular sites, prodrugs, and novel formulations).

- REMS could encourage appropriate prescribing or unintentionally drive prescribing to less optimal drugs and drive abuse to other drugs.

His major conclusions and recommendations:

- Central nervous system (CNS) drugs pose special challenges for risk management related to possible abuse liability.
- CSA (Controlled Substance Act) scheduling is a form of risk management that needs to be harmonized with current risk management strategies.
- Preclinical and human abuse liability testing has good predictive ability for real-world abuse of CNS-active medications and can thereby serve CSA scheduling and REMS development.
- Traditional surveillance surveys do not provide the timely, sensitive, and accurate information required to guide the iterative process.

Community Hospices of Washington DC, Maryland, and Virginia. Hospice nurses Diana Davis and Jill Jackson described **how their hospices control opioid abuse**. Davis said, "We attend every patient death, and we have a medication disposal record. We count every medication, every liquid. We then melt that medication, and we pour it onto solid waste or paper towels so we do destroy those medications." Jackson added that OxyContin is critical for patients who are dying. In some homes where her hospice sees a potential for abuse, Jackson said lockboxes are used to contain opioids and other drugs.

CVS Caremark. Stephen Heidenthal, director of pharmacy operations at the company, which is the largest provider of prescription drugs in the U.S. (with four million customers a day), called for **consistency and standardization for all REMS** and said that an opioid REMS must be fully compatible with current systems for other REMS.

On pharmacist education, he said, "If it is deemed that pharmacist training is necessary, we recommend the use of the training providers in place today. Pharmacists should be personally responsible for completing the course. There should be no requirement to take the opioid education program more than once."

On patient education, he said:

- Physicians are best equipped to determine if the patient has been educated before prescribing. Pharmacists are here to support patient education in all medications. Unique materials distributed to patients should be universal document class – one concise document that is flexible.
- Distribution of MedGuides to pharmacies should be integrated in systems that provide electronic data to pharmacies today. Printing and distribution of MedGuides cannot be sustained without reimbursement.
- Must be available by an automated process without pharmacists having to stop.
- We do not recommend any patient education as a condition of receiving an opioid.

How restrictive should a REMS program be? He said CVS does not support limiting the REMS to select healthcare settings. He said pharmacies already operate under some of the most restrictive rules, and CVS does not support additional requirements/restrictions.

He summarized:

- If required, CVS recommends integrated verification qualifications.
- If required, pharmacy education should be by continuing education providers and linked to state licensing processes.
- CVS does not recommend patient registries or verification of patient education.
- CVS is against restricted distribution sites.

The FDA's Dr. Jenkins asked, "We've heard suggestion linking requirements to the DEA system. In your system, how do you verify DEA registration? Is that automated?" Heidenthal answered, "We use a multitude of switches, such as RelayHealth, and that uses National Provider Identifier (NPI) numbers and DEA numbers. That's all automated through the adjudication system, and it is an instantaneous process."

Dr. Jenkins then asked, "Does it allow you to verify if it is a Schedule II prescription? Verify that the prescriber has Schedule II in a DEA registration? Do you verify that?" Heidenthal answered, "Whether that is exactly verified, I have to get back and check. The capability is tied to a class of drugs and is capable of doing that."

The FDA's Dr. Throckmorton asked, "You mentioned or proposed using current continuing education programs available. How do they assess their success? Do pharmacists need to take a test at the end? Or is it a sign in, be there for a period of time, and get a certificate?" Heidenthal responded, "For the timing that's required to roll this out, you probably want to leverage distance learning – a document you have to read and answer a test. The alternative is a live audience setting, and you sign in and are present for a period of time."

Denver Health and Hospital Authority. Elise Bailey, RADARS system operations/business manager, described the application of the RADARS system data to evaluation of a REMS. The RADARS system addresses every part of the drug pathway, from experimentation to addiction and remission. She then presented an analysis of the Kentucky Operation Unite program in eastern Kentucky. She recommended:

- Evaluation from multiple perspectives is essential (drug diversion provides a unique perspective).
- **Implementation of a REMS should be considered for immediate-release opioids**.
- Immediate-release opioids should be a comparison group to extended-release opioids.
- RADARS data can evaluate intervention and effectiveness of REMS and should be thorough enough to identify the squeezing of the balloon phenomenon.

Healthcare Distribution Management Association. Anita Ducca, senior director of regulatory affairs, urged the panel to be cautious as it proceeds with regard to two potential controls: (1) Requiring distributors to verify customers, and (2) Requiring after-the-fact reports on what has been distributed to whom.

She said that "**distributors are not in a position to remedy the abuse and misuse problems**. We don't deal with patients. A REMS that requires a distributor to verify a customer would duplicate existing controls under state and federal laws and DEA and state registration and license verification. More than 75% of drugs arrive though distributors. Eight million products are distributed every day, and a typical wholesale distribution warehouse delivers to more than 1,000 dispensing sites daily. Any change in how we distribute would present significant difficulties to the smooth distribution system that has been in effect for years. We've noted errors in a much smaller (REMS) system, and there is potential for disruptions in providing opioids and products not covered by the REMS. Certain requirements for other REMS that FDA may establish for opioids may not be sustainable…It is not appropriate to require distributors to require after-the-fact reports showing what has been distributed and to whom. Distributors already make three reports to the DEA, and reporting additional data is not an appropriate step because it would require substantial IT (information technology) modifications and disrupt distribution. Smaller distributors often have more limited IT capabilities, and the REMS may have greater impact on them and on their customers, which tend to be independent pharmacies and located in more rural areas."

The FDA's Dr. Throckmorton asked, "Why are the reports not something we should think about? I heard several arguments. One is, 'We already give you reports that contain everything you need.' The second argument we hear is, 'We're not going to give you any information you need.'" *(laughter)* Ducca responded, "We don't see patients, and so we have no ability to reconcile any of the distribution that we do with any of the prescriptions that are filled. We don't touch on patient prescribing behavior, so we are not going to be able to give you data that would reveal any of the kinds of success stories that you are looking for in a REMS. As far as the duplication goes, DEA requires very extensive reporting. Every single order for a product we receive must be received on Form 222 from the DEA, which includes the name of drug, who is ordering it, quantity, wholesale distributor name. All that is placed on the form in triplicate, and the DEA gets a copy of that form. They also receive ARCO's (Automation of Reports and Consolidated Orders) reports at least quarterly. The DEA already has everything we could imagine that you would want from us. The suspicious reporting report – if an order comes in that looks like it is following an unusual pattern, unusually large, we report that to the DEA, and we don't ship until we at least investigate that report."

Health Care Notification Network (HCNN). Dr. Henry DePhillips, chief medical officer, said that **existing systems, relationships, and processes can be used** to implement the opioid REMS. The new steps include a standardized prescriber patient contract signed and placed on a patient's chart, a prescriber certification program (followed by documentation of prescriber knowledge and certification). He said, "Dispensers need to confirm that the prescriber is certified before filling the prescription."

He cited three elements to ensure successful execution of an opioid REMS:

1. Be careful about prescriber perception – include prescriber liability protection, certification credits.
2. Ensure prescriber participation, so the number of prescribers doesn't go down.
3. Dispenser confirmation. There is an existing expansive electronic system which all pharmacies currently use. Dispensers can check prescriber certification at the same time.

Kendle Early Stage, a clinical research organization (CRO). Dr. Edward Sellers, vice president, said that his company has conducted 50 Phase II and III clinical trials involving opiates, evaluates REMS programs, and is conducting more than a dozen post-marketing surveillance registries. He said that a REMS is generally used to assure the public of a product's safety, "However, what patients and doctors want to know is whether it is the safest and most effective drug for the patient."

Information from a REMS can be slow to be recognized. So pre-approval studies are recommended among similar products or different technologies, asking people how they'd tamper with drugs. These kinds of studies provide robust data

that allows adjudication prior to marketing as to what the post-marketing risks might be. Specific releases are likely to be different with a patch compared to an extended-release product, etc. To date, the methods of post-market surveillance relied on large data sampling, (i.e., the RADARS system), but there are a number of limitations to these methods, including timeliness, and reliably detecting abuse/addiction of opiate medications is extraordinarily difficult. It's relatively rare compared to the use of these products. Measuring abuse outcome, measuring cross-sectional populations, is neither appropriate nor feasible."

McKesson's RelayHealth, a healthcare network solutions company. Roger Pinsonneault, R.Ph., senior director of project management, said one of the FDA's questions is, "What systems already exist that could be used to implement a REMS?" Pinsonneault said that **his company's system could be used to implement a REMS**. He said, "It already exists. Twenty million prescriptions a year is a small volume relative to what we are doing now. More than 55,000 retail pharmacies go through RelayHealth, and on to payers for claims adjudication."

RelayHealth is a neutral real-time network and does more than 70% of pharmacy claims adjudication, with around 11 billion transactions processed annually. It uses a 36 terabyte SAM. It also has a number of controlled substance reporter services that it offers to pharmacies. RelayHealth avoids telephony-based verification activities, card-based verification activities, and web portal-based verification activities.

Pinsonneault suggested:

- A standard processing model for all REMS programs.
- Class-wide opioids.
- Physician verification activities including DEA's Prescriber ID and state-specific activities until the universal migration of the National Provider Identifier (NPI) is achieved.

He said that his company has six pharmacy customers, representing 26,000 pharmacies, and five of the six recommend that the FDA move to his company's business model.

National Association of Chain Drug Stores (NACDS). Kevin Nicholson, a pharmacist and vice president of government affairs and pharmacy advisory for NACDS, called for **standardization in REMS** in order to help ensure success.

On pharmacist education, he said NACDS "believes that pharmacists are fully qualified to fully dispense all opioid products, and **additional education requirements are not necessary**…If the FDA insists (on pharmacist education), state programs can be established."

Patient education, he said, "should be at the point of prescribing. It is at the physician's office where the patient is evaluated. The patient should not have to wait until reaching the pharmacy to learn about risks and benefits."

Nicholson urged the FDA to "first finalize the one document solution for written prescription information, rather than requiring new consumer information, package inserts, or medication guides."

How restrictive a system? He said:

- "Pharmacies are already highly regulated, and we see no need for additional regulations. A limited distribution system would only shift problems rather than solve them.
- "Patient registries should be avoided. They have been difficult to administrate…and that was for one chemical entity. The TOUCH program has many administrative hurdles that must be met before the medication is dispensed.
- "A REMS should not include controls on distributors.
- "Since the REMS would apply to a class of drugs and may expand over time, its implementation must be seamless and not hinder pharmacy workflow. Options include FDA working with pharmacy transaction switches or prescribing intermediaries."

National Council for Prescription Drug Programs, which represents the pharmacy services sector of healthcare. Phillip Scott, senior vice president, said, "The answer to the question – 'How can the FDA act quickly?' – is to **leverage the technology** that is available today."

Vitas Innovative Hospice Care/Palliative Care Solutions. Dr. Joel Policzer, a fellow of the American Academy of Hospice and Palliative Medicine (AAHPM), said that a REMS for opioids "**will have a chilling effect on the terminally ill**. Physicians are reluctant to prescribe these medications already, and we will see a decrease in adequate pain management and a further obstacle to appropriate end-of-life care."

Some of his recommendations:

- Exempt any patient enrolled in a licensed, certified hospice or palliative care program from the REMS (average length of stay is 67 days; median length of stay is 14 days).
- Any physician credentialed to care for end-of-life patients in hospice or palliative care service should be exempt from REMS regulations when providing care to end-of-life patients.
- Diversion is a very small problem in these patients and in the families.

- Recognize that ongoing clinician/patient family education regarding these medications via CMS regulation. The new Conditions of Participation for hospices require ongoing discussions on these medications and side effects, etc.
- It would be acceptable to have limited dispensing (maximum 15-day supply or to allow partial fills).
- When any change is made in opioid therapy, any existing doses will be disposed of real-time (i.e., a take-back program).
- Development of a dispensing pharmacy national clearinghouse. All pharmacies would be interconnected to be able to know how many prescriptions of each medication have been filled for each patient.

Asked how many physicians are credentialed for hospices, Dr. Policzer said that more than 500 physicians are credentialed in his organization's 45 hospices. The FDA's Dr. Throckmorton asked if there is national credentialing for such doctors, and Dr. Policzer responded that Hospice and Palliative Medicine became a recognized subspecialty last year, and the first board certification examination was in October 2008. Dr. Throckmorton asked if licensure is dependent on demonstration of a proficiency of any kind, what criteria are used, and Dr. Policzer said the licensure is state-by-state, but most certification is through CMS, and there are criteria that have to be adhered to when one makes the application for CMS in order to bill Medicare. There is also onsite evaluation and ongoing evaluation.

Dr. Throckmorton asked if in certain long-term facilities the end-of-life group is mixed in with other patients, and Dr. Policzer said that they don't need to be separated, but some facilities choose to separate them because of patients' special needs, and some believe that it is easier to care for end-of-life patients when they are separated.

Asked if the practice of using lockboxes is routine, Dr. Policzer said, "Not in my experience. In my experience, diversion is a very small problem. My recollection…is that it happens relatively infrequently. There are various solutions, including observing the taking of the medication. There are solutions, and we solve it on a case-by-case basis."

Epidemiologist Nabarun Dasgupta, a researcher at RADARS System and the University of North Carolina School of Public Health, said that an **opioid REMS is different from other REMS** in several ways:

- Opioids are multiple drugs vs. traditional REMS, which are for a single drug.
- Social context (geographic specificity, policy bank, other influences).
- Outcome specific (abuse, misuse, addiction, and overdose).
- Effect in patients and non-patients.

He predicted that an opioid REMS will affect equitable access to care, adequate pain control, quality of life, end-of-life care, and may result in a healthcare system burden, "Abuse, misuse, addiction, and overdose do not have the same etiologic factors and cannot be measured together…Efforts to control one outcome may have a paradoxical effect on other outcomes (i.e., shifting from addiction to abuse increases overdose potential in non-patients)."

His recommendations:

- Specify the evaluation plan *a priori.*
- Define how much is acceptable.
- Measure in patients and non-patients.
- Select proper comparison groups (include generics, immediate-release, heroin).
- Acknowledge and monitor other influences.

INDUSTRY WORKING GROUP (IWG)

Three speakers from the Industry Working Group, a consortium of 25 companies that market extended-release opioids, told the panel that it is working on a class-wide REMS.

Dr. Eric Carter, chief science officer for King Pharmaceuticals, said that the keys to a successful REMS are:

- Adequate pain control is essential to good medical practice.
- Under-treatment of pain is a common problem.
- Addiction and death due to prescription opioids continue to increase.

Dr. Carter said, "For the vast majority of patients, these therapies are effective, safe, and well tolerated. Balanced against this is the secondary health concern, and this recognizes the trend toward the misuse and abuse of prescription opioids leading to death, poisoning, teen suicide, etc…The problem is not getting better and may be getting worse…We recognize the need to redouble our efforts to reduce opioid abuse."

He said the IWG timeline has been:

- February 6, 2009 – FDA sent a letter to sponsors.
- March 3, 2009 – Meeting between extended-release opioid manufacturers and the FDA. The FDA asked for a single strategy that would reduce the risks associated with the products.
- March 26, 2009 – First IWG teleconference.
- April 7, 2009 – First face-to-face meeting for IWG:
  - Scope of IWG defined.
  - Operating structure discussed.
  - Criteria established to draft a charter governing IWG.

- Action plan agreed on – IWG would be comprised of brand and generic manufacturers.

➢ May 13, 2009 – Proposals were presented, including an anti-trust counsel, IWG charter, third-party vendor for project management, sub-team presentations for initial REMS recommendations, and agreement on FDA public meeting.

Dr. Carter complained that some manufacturers were not given the opportunity to attend FDA stakeholders meetings until this hearing, "We need a constructive dialogue with ***all*** parties to succeed."

Dr. Craig Landau, chief medical officer for Purdue Pharma, detailed the IWG's REMS proposal. He said the REMS goals (according to the FDA) are:

1. To ensure that the benefits of the drugs continue to outweigh the risks through proper patient selection, minimizing the risk of overdose, both accidental and intentional, and minimizing the risk of abuse.
2. To ensure that prescribers, dispensers, and patients are aware of and understand the risks and appropriate use of these products.

Dr. Landau said that for a REMS to be successful it must not interfere with the ability of prescribers and other healthcare practitioners to effectively treat patients in pain, but little to no evidence exists supporting the ability of existing REMS tools to reduce abuse, "The selection of REMS tools should be designed so their effect can be measured. Success targets should be predefined." He said the challenges are:

- Abuse is a long-standing societal issue.
- Addiction is a complex, multifaceted behavioral problem.
- It is difficult to balance the desire for a rapid REMS rollout with the concern for unintended consequences for patients, prescribers, dispensers, and other stakeholders.

REMS components on which the IWG has agreed:

➢ **Medication guide.** However, concerns were expressed about the usefulness of this tool in its current form. Dr. Landau said, "We want to make these documents more readable and more informative."

➢ **Brief patient guide.** The IWG also supports the creation of brief patient guides including a tear-away wallet card, but Dr. Landau noted, "We don't know how effective they would be or how they would be accepted by prescribers, dispensers, and patients."

➢ **Communication plan.** The IWG communication plan includes a "Dear Healthcare Provider" letter, a "Dear Pharmacist" letter, letters to professional societies, trade journals, state licensing boards, the Federation of State Medical Boards, the DEA, and the FDA.

➢ **Elements to assure safe use.** Dr. Landau said, "The working group strongly supports education and training. We have looked at prescriber education. Education of prescribers (and pharmacists) should focus on risk mitigation strategies and be offered in various forms. The programs should be tested to ensure they meet the desired outcomes. Specifically, knowledge acquisition and application and continuing education credits…should be given. We believe that the source of the educational content should be from professional organizations, not industry and not government." The elements would include:

- Prescriber education, training and certification.
- Dispenser education, training and certification.
- Prescriber-patient agreements. Dr. Landau said that the IWG supports a signed prescriber-patient agreement, "Versions exist, but the agreement would be developed to ensure that the patient would discuss with the provider the benefits and risks…and would provide guidelines that enforce the seriousness in which drugs should be handled."

➢ **Implementation system and timetable for submission of assessments**. This would include stakeholder surveys (REMS efficacy, burden on healthcare system, impact on patients, etc.) as well as status reports.

Stakeholder participation needs to be broad and sustained, with prescriber and dispenser participation essential, Dr. Landau emphasized. He noted that industry's reach is limited and urged leveraging the existing DEA registration process to reduce the burden, extend the reach, facilitate participation, reduce the likelihood for patient access problems, etc., "We heard that industry should not design and control education and training, and the IWG agrees completely with this concern. DEA involvement, including REMS-mandated education and training, should be part of existing DEA registration. It would be the least burdensome on physicians and dispensers and would ensure that bias would be removed …All prescribers would meet requirements for DEA registration. The verification would simply be added to valid state medical license and the state controlled substance number."

Finally, he said that the technology burden and risk is of an unprecedented magnitude, "The REMS we are discussing is obviously very different from any REMS or marketed product. For example, in 2008, about 20,000 prescribers wrote more than one million subscriptions for Accutane (isotretinoin), branded and generic. In the same calendar year, 375,000 doctors wrote nearly 26 million prescriptions for extended-release opioids."

Martin Lessem, senior regulatory associate, Ranbaxy Laboratories, said that the next step for the IWG is to get other stakeholders involved, "The IWG can't work in a vacuum…While the FDA touts the efficacy of iPLEDGE (the

REMS for Accutane), it is still pending approval. There are still outstanding questions…IWG wants to work with stakeholder groups, including prescribers, dispensers, benefits management groups, patient and advocacy groups, the DEA, and other government agencies. We couldn't meet with the other stakeholder groups. We need your direct input to make this program a success. The IWG would like to reach out to the DEA and other government agencies. We also would like more engagement on a regular basis with the FDA. We are asking for a meeting after the comment period, and we want to do a study – an initial test of the REMS. iPLEDGE went through three iterations before what it is today. We would like to discuss a pilot study program."

The FDA's Dr. Jenkins said, "We heard a lot of calls for immediate action, but we also heard calls to get it right. It's important for the IWG to tell us what immediate actions can be done to address some of the concerns while we work through the long-term actions to get it right."

The FDA's Dr. Throckmorton asked if the IWG is in support of the prescriber-patient agreements, saying that he had heard something different at the first day of this public hearing. As for using the DEA's registration system as a model, Dr. Throckmorton said, "You talked about using state licensure as the place to assure education. And then if state licensure were obtained, the DEA registration would follow. That disaggregated system is there instead of using the DEA system in place. Whichever model you choose, a discussion of how you came to choose that would be helpful."

The FDA's Dr. Dal Pan asked how the REMS would be assessed and how misuse and abuse would be assessed, as well as access to medicine, and other FDA officials offered comments.

- *Jane Axelrad:* "I would hope that you will specifically address how you would do a pilot program. We had a lot of discussion about that."
- *Dr. Jenkins:* "We had a lot of calls for pilot programs and a lot of calls for immediate action, so what are the immediate actions that could be taken while working through long-term solutions? We heard about what was referred to as a moratorium on prescribing and use of certain extended-release pain medications, and we heard about pilot programs. We've heard a lot of views about need for action, and we're hearing a lot of stakeholders say, 'Don't do anything until you get it right,' and we need to find a right balance."
- *Terry Toigo:* "We heard from a couple of patients that they signed agreements, but they weren't educated. How do you ensure that the agreement makes a patient feel educated after signing it?"

SHOULD METHADONE HAVE A SEPARATE REMS?

Kimberly France, director of product and patient safety at Covidien, talked about obstacles to a single shared system and said that the current process favors innovator companies. She and another speaker told the panel that methadone should have a REMS separate from the extended-release opioids. However, the body language from the panel (heads shaking left to right and eyes rolling) indicated that the idea wasn't received well. The two speakers were queried about how they could be part of the IWG but still want a separate REMS, and France responded, "The overriding question is how to advance patient safety through a REMS that is equitable, fair, and not prohibitive to stakeholders and especially to patients who do not have prescription drug coverage or cannot afford brand products."

France said that her company hosted a meeting of generic manufacturers on April 20, 2009, and they agreed:

- In a single shared system, REMS should be grounded in patient safety, not simply to mimic the innovator's program.
- Prescriber training in REMS should not be provided by the sales force.
- ANDA holders should have input into the communication plan.
- Medication guides should be developed collaboratively between brand name and generic companies.

Elizabeth Ernst, director of medical and regulatory affairs for Roxane Laboratories, said that methadone should have its own REMS because it:

- Is not formulated as "sustained-release" like other opioids.
- Has both pain and addiction treatment indications and is used in multiple settings. The other products are limited to pain indications.
- May prolong the QTc interval, which could lead to Torsades de pointes, which is not associated with the other products.
- Has activity at the NMDA receptor, unlike extended-release opioids.
- Is the subject of pending legislation (Methadone Treatment and Protection Act of 2009).

Ernst told the panel that Roxane intends to submit a REMS proposal for methadone, which

- Builds on efforts of SAMHSA and DEA.
- Requires prescriber training and training for staff in healthcare settings where methadone is dispensed such as clinics.

- Requires a medication guide addressing unique indications and providing patients needed information that they can understand.
- Implements a system with better monitoring of methadone starting and maintenance doses and identification of special populations while maintaining privacy.
- Has a shorter timetable for assessment.

Ernst said Roxane will work collaboratively with manufacturers of long-acting opioids to effectively address patient safety; will identify solutions that address patient safety, minimize burden to healthcare providers, and maintain patient access to these needed medications; and will have early, active, and transparent communication with regulators.

FDA questions

FDA officials had questions for both France and Ernst on their proposal to have a separate REMS for methadone. The FDA's Dr. Hertz said that a common theme that the panel heard on the first day was to keep all opioids under one REMS. France answered, "There are different elements of the REMS, and there is a way to have one or more of the elements that are consistent and shared across a broader group of products while still having elements of a REMS that are unique to a specific process. Also, methadone has indications and treatment settings that are not equal to extended-release opioids."

- *Axelrad:* "I'm confused. I thought a lot of your comments were addressed to how other REMS have worked, and since generics are part of a broader working group, everyone is planning to work together. I want to make sure that I understood. That was our intention when we invited all the sponsors to the meeting in March."
- *France:* "We weren't making the statement that this process has not been inclusive or collaborative, but our past experience with past programs and prior to this experience had not been in that same collaborative vein."
- *Dr. Throckmorton:* "Different from the formal process that you have constructed now? What process are you talking about?"
- *France:* "The previous experiences – specifically, the RiskMAPs – didn't have a process for convening both parties with the exception of iPLEDGE, which we were not involved in. We have been left to find our own way …The point is that we need a formal process. To move forward with any kind of class-wide REMS, there has to be some guidance as to how, as companies, we can work together so we don't have to figure it out each time."
- *Axelrad:* "In a way, this is a pilot program. We can learn some lessons from this experience and then apply it later as we start thinking about giving some guidance in the future about how companies can work together."
- *France: (laughing, but the panel members were shaking their heads and looking grim)* "Those comments will not make the June 30 deadline."
- *Dr. Dal Pan:* "It would be helpful (for you) to expand on how generic drugs are distributed."
- *Dr. Jenkins:* "The IWG participants' slide included Covidien and Roxane, and your presentation is suggesting a REMS, separate from the other REMS, for methadone. Is this a dissenting opinion from the IWG presentation? How does your presentation relate to theirs?"
- *France:* "As the IWG goes…we are supportive as we hold ANDA applications…But for the reasons that methadone is unique to the other five products in the basket, it should have a separate REMS. That does not preclude us from having shared or common elements such as prescriber training, but the actual implementation, reporting, surveillance, and evaluation of methadone would be separate in total and submitted by the methadone manufacturers and not by the IWG."
- *Ernst:* "We support and stand by the IWG. The reason for our discussion about methadone is that methadone is used for two very different indications – one for pain and one for addiction. If you put it in the REMS for extended-release opioids, you've missed the indication. There are seven of us, and we think we can provide and initiate a program maybe quicker, and they can be part of the bigger program from IWG."
- *Dr. Rappaport:* "We would appreciate you addressing how you're going to interface the current regulations that exist for the addiction treatment use side of this with a REMS and whether that's even necessary. It seems a difficult and complicated task."

Suggestions About What Should Be in the REMS

Twenty-one speakers offered their ideas about what should – and should not – be in the REMS.

American Medical Association (AMA). Dr. Ardis Hoven, a Kentucky internist, said that **physicians need better training on pain management**.

- The AMA favors the use of positive incentives to encourage physicians to complete education courses.
- The FDA should promote alternative strategies that do not hinge on manufacturers to implement and maintain the system.
- The AMA's 12-hour CME program on pain management is an excellent tool.
- Any education or certification requirements of opioid REMS should include the input of practicing physicians.
- When risk management beyond product labeling for a specific drug is needed, an intense communication plan must be tried first.
- Mandatory education and certification can only be used as a last resort to keep products on the market.

- Unintended consequences of a REMS could include physicians opting out, with fewer physicians willing to manage patients with chronic pain.
- Doctors may be confused by the REMS.
- The AMA opposes mandatory practices that are already considered appropriate in certain patients, including patient-physician agreements and urine tests.
- The FDA must have appropriate metrics in place.

The FDA's Dr. Rappaport asked if the AMA is aware of any data to support the statements that the negative impacts she listed may occur. Dr. Hoven said, "A lot of this may be anecdotal, but we need baseline information to tell us whether elements of the REMS are really going to make any difference at all."

American Society of Pain Educators. Dr. Eliot Cole, executive director, said, "We are going to have to see a change in how we do business for REMS to work. One bench-line metric might be what **baseline level of mortality** is acceptable. A decrease in prescribing doesn't necessarily translate into fewer problems because the people engaging in criminal activity, misuses, abuse, diversion, can always get what they want; only the price point changes. And people in pain will suffer from lack of medicine…Will we have to do a REMS down the road because of this REMS? The government has never been able to legislate against driving a car too quickly or in an unsafe fashion…The 800-pound gorilla is that the DEA will not do anything about diversion if it doesn't involve non-criminal intent…So, other than death and the horrors of addiction, I can't figure out what the consequences are."

Dr. Cole said that education "may be what we have going for us. We are going to have to look at sticky messages and look at multimedia focus group-tested methods to communicate more effectively. Patients need messages that they can go home with that tell them how to take medications carefully and dispose of them properly. Also, many prescribers can be better versed in pain management."

He asked FDA officials why the Agency doesn't approve the new tamper-resistant drugs. He asked why people are talking about the DEA when the DEA is not under the FDA's jurisdiction and won't do anything unless ordered to by the government. He suggested collaborating with another agency, like the Department of Homeland Security (DHS), which he said is interested in narcoterrorism.

Aventine HealthSciences, a medical communications firm. Stephen Porada said that RiskMAP approaches will not yield different outcomes under a REMS label. The **patient must be actively engaged**, exposed to safety messaging in a variety of ways, including outside the doctor's office and pharmacy.

BearingPoint. Karla Sticker Anderson, managing director of Life Sciences Commercial Operations, and Dewey Seto, manager, recommended that the FDA should consider an **extended program development period** for the opioid REMS program "due to the unprecedented level of multi-sponsor involvement which dramatically impacts two key areas of program development including:

1. The program development decision processes coordinated across multiple manufacturers.
2. The program operations and data interfaces among REMS vendors and the reporting processes.

Anderson said that a good, balanced program development would need a multidisciplinary team from each of the manufacturers.

Asked how much time it would take, she answered, "A year as opposed to 120 days, and try to look at it from the ground up." Asked if that's from development to implementation, she said, "Realistically you could build a foundation in a year, pilot even multiple operational models and evaluate them, but you couldn't have a fully operational program in any time less than that." The FDA's Dr. Dal Pan asked, "Are there any existing programs that could be used? You're adding in existing company processes. It would be helpful to know what those processes are and where they interface with the external systems."

Catalina Health Resource. Suzanne Eastman, executive director, clinical services, said that physicians should counsel patients, but that **pharmacists also should be responsible for counseling patients and distributing pamphlets**. Eight stakeholders, including her company, are petitioning the FDA for an FDA-approved plain language document that would combine and simplify current documents patients receive in the pharmacy about prescription drugs.

- *FDA's Axelrad:* "Obviously we need to identify what methods should be delivered."
- *Eastman:* "We have a mechanism now for delivering the message directly to patients. We also have a mechanism for delivering the method to pharmacists, and we have implemented that."
- *Axelrad:* "What pieces of information are given when prescribed, and what pieces of information are given when dispensed?"
- *Eastman:* "There are so many prescriptions that never are filled at the pharmacy, and the patient needs information …that doesn't scare the patient into never filling the prescription. The patient needs to understand the need for filling the prescription, while encouraging compliance and adherence…Then, give that patient avenues and information about where to go if they experience a side effect or adverse event or if they need to dispose of the medication. There would have to be different messages crafted for those different points."

- *FDA's Dr. Throckmorton:* "We would like to see some evidence of methods and metrics used to assess the success."

Clinical Marketing Consortium. Dr. Richard Slattery, president, said that his company has conducted about 30 post-marketing programs over the past 20 years. He described a Phase IV study for a Schedule II opioid on which he worked with a sponsor, and it took nine months to develop the protocol. Two objectives of the study were to assess the potential for misuse and abuse of the opioid and to institute and measure a "universal precautions" approach to pain management, utilizing treatment agreement, patient screener, urine drug test, and a doctor/patient/pharmacist tracking mechanism. He said that the lesson from that experience is: "There are solutions available for a class REMS that **require multiple participants**."

Inflexxion. Simon Budman, president/CEO and a clinical psychologist, said that **substance abuse treatment centers can be an important metric for measuring REMS success**. He said, "At a 3-digit zip code level, the average correlation between prescription opioid abuse among patients entering drug treatment and medical opioid availability is .70." He helped develop a web-enabled, real-time system to capture prescription drug data from adult and adolescent abusers entering treatment (sentinel population). Nearly 500 sites use the system nationally, with 20 new sites joining each month. Every center in New Mexico is using the program. They use both ASI-MV and CHAT for their own purposes. The interface is Addiction Severity Index ASI-MV Connect.

Budman told the FDA members, "We find that extended-release and short-acting opioids are similar problems, and we must look at both." He concluded:

- Substance abuse data will be crucial in evaluating REMS outcomes.
- Critical data are needed from adults, adolescents, and minority populations. About 10%-15% of data are from Spanish-speaking patients.
- Data collection requires seamless integration with clinical workflow.
- It is necessary to evaluate unintended consequences (e.g., the effect on heroin abuse rates in treatment center data as new REMS are introduced).
- New Mexico, where there was total coverage, would be an excellent place to do a pilot program and see the effectiveness of a REMS that is statewide.

The FDA's Dr. Throckmorton asked if there are any states besides New Mexico that are using the program to track for abuse. Budman said, "The states using our system are generally using them for other purposes – for resource allocation, to better understand the substance abuse populations and the effectiveness of substance abuse programs."

Dr. Kevin Zacharoff, director of medical affairs for Inflexxion, talked about **pain education initiatives** for providers, patients, and vulnerable population and the role of education in a successful REMS. His company's products, PainEDU, painACTION, and MyStudentBody are prevention and intervention programs focused on education providers, patients, and vulnerable populations for risk mitigation.

John Glover Consulting. Dr. John Glover, doctor of public administration (DPA) and president of this pharmaceutical security firm, said that many factors contribute to illegal diversion. Two key factors are (1) lack of source information that can be gleaned from confiscated products, and (2) the distribution system allows cross-state shipping of opiate products.

Dr. Glover said that, from a law enforcement perspective, in the case of illegally diverted opiates, "The investigation at hand is usually minimal given that the medication is repackaged and carries no information as to the intended site of distribution, so the lack of source information presents a challenge for law enforcement and government agencies… REMS programs have focused on patient and prescriber education. While these are important, opiate products require a more specialized mitigation approach such as **on-dose technology**. It is important to go beyond the traditional education-based approach for opioids. Opiate products have RiskMAP programs with education and outreach programs, but these have failed to control the abuse and more is needed. For dose-level tracking and tracing, it is important to consider that dose technologies don't require equipment or a downstream supply chain to be effective. Since the technology relies on each dose, repackaging has no effect on tracing information. The information associated with certain on-dose technology is virtually unlimited."

NanoGuardian. Jim Hussey, a pharmacist and CEO, said, "Until we can come to an **understanding of who the non-patients are** and separate them from the patients, a lot is being clouded. Common activity between generics and brands are important, and the FDA has to work down at the zip code national level to track these products. At the local level, is diversion occurring, what is happening, who is doing it? And that has to be taken into account when assessing the progress of a national program. We don't have data to find out what the non-patients are doing."

Hussey said that while REMS up to now have been focused on patient-physician education, the opioids REMS will have to deal with diversion and illegal use, "One reason they (opioid risk management programs) have not been effective so far is the inability at the local level to assess diversion. REMS should include additional plans for product security, the ability to track through the system, and to track the pill. Non-patients don't keep the packaging."

He suggested a dosing security program, "We believe that forensic-level nanocodes provide tracing information on every single dose. We do know from reports from police that there are illegal products entering from outside the U.S. We don't know if it's a domestic problem, an importation problem, etc…On-dose technology would be a powerful new tool to track the products: Are they in the system, outside the system, in the right place? Each of the 110 wholesalers in the U.S. can provide information to us about exactly what's happening to them. A bag seized in Florida could contain enough nano-information to tell us exactly what's happening."

ParagonRx. Jeffrey Fetterman, president, talked about using **failure mode and effects analysis** to assess and prioritize risks for intervention. He said that it will be challenging to integrate all the opinions heard at the meeting. His company convened a small working group after the stakeholders FDA meeting to see if there might be a better way to identify where potential efforts could occur in the process as a way to target interventions. His model shows a five-step process of prescribing and dispensing opioids with 25 sub-process steps, "So there are many ways in which the current process can fail, and there are many underlying causes of failure. Of the 25 sub-process steps, there are 50 possible causes of failure."

FDA officials were very interested in his model and said that they looked forward to seeing some of the information published in the docket.

Some examples of the failure mode:

- **Step 1:** New patient medical records not available at point-of-care. Potential causes include:
  - Healthcare professional misunderstands the need to identify opioid-naïve patients.
  - Partial/incomplete medical records or history.
- **Step 2:** Healthcare professional inaccurately interprets patient risk/prognostic factors.
  - Partial/incomplete medical records or history.
  - Patient has multiple comorbidities (i.e., depressed).
  - Healthcare professional fails to properly assess the continuum of opioid use and response over time.
  - Healthcare professional lacks experience.

Fetterman said that design principles include targeting interventions to potential causes of failure.

- Cause of failure drives specification for intervention.
- Redundancy mitigates failure by a single stakeholder using a single tool.
- Education across multiple stakeholders, education backed up by enabling tools (checklists), and addition of controls.
- Some causes of failure need a specific tool.

The FDA's Toigo asked, "You just gave us a magnifying glass for our daunting task. Will you publish this?" Fetterman responded, "We will complete our analysis in the next four to six weeks…We will publish our progress as the deadline docket approaches."

Parexel Consulting. Ravi Haranpanhalli, principal consultant and late stage services lead, said that the REMS should include **controls on distributors** in order to prevent diversion and counterfeiting. He recommended that enhanced electronic readouts be included on the REMS.

He suggested **mandatory opioid barcode labels**, pointing out that barcoding is a requirement for some prescription drugs, such as blood and blood component products, and asking, "Why not opioids?" The barcodes could use Standardized Numerical Identifiers (SNIs) to identify individual prescription drug packages and to facilitate authentication and the tracking and tracing of the prescription drugs.

Pinney Associates. Vice president of pharmaceutical risk management Dr. Sidney Schnoll, a professor of internal medicine and psychiatry at Virginia Commonwealth University, treats addiction and pain. He said that prescription drug abuse has been a problem for a long time, "When we're dealing with a problem like addiction, we need balance…We heard a lot of people talk about balance, but I'm talking about balance between the supply side approach and the demand side approach. We haven't heard a lot here about **addressing the demand side of addiction**. So, we have to ask if REMS are the right approach…Now, we're going to be asked to demonstrate that a REMS will have an effect on non-patients."

He admitted that REMS are here to stay but posed a number of questions.

- What will be the impact on patients? Will it be harder to get medication? Will prescribing decisions be based on REMS or patient need?
- What will the impact be on healthcare providers? Will the impact be different for different providers? Will some providers opt out? Will there be changes in prescribing patterns? What needs to be measured, and how might it be measured?
- Who is responsible for non-patient abuse?
- How are patients different from non-patients?

Asked if he's against the REMS, Dr. Schnoll answered, "We need to go forward and address the issue, but we have to address it carefully. One way you might want to approach a pilot project would be not geographically, but you might take a product like methadone and apply some of these tools to that product. Certainly, none of the things included in the REMS has been studied for its effectiveness. We need to make some strong but careful decisions."

- *FDA's Axelrad:* "We have heard that much of this has been studied in small areas, many of these kinds of controls."

- *Dr. Schnoll:* "You have to be careful when you take something that has been done in a small study and scale it up, especially in a REMS of this size."
- *FDA's Dr. Rappaport:* "Do you have any recommendations for tools or metrics that we could use to measure some of these positive or negative impacts?"
- *Dr. Schnoll:* "I've been thinking about it…An example we've heard about is the effect of putting benzodiazepines in New York in Schedule II. We need to look at some of these ancillary type things. We have to think about them, but we also have to come up with how much of a change is a significant change, and that's another problem. Do we have the ability to measure that?"

Rienzi and Rienzi Communications. Frank Gallo, vice president and general manager, discussed patient communication beyond the medication guide. He answered a physician-patient agreement question from the FDA, "The answer is yes, we agreed that the **physician-patient agreement** should be signed and captured by, or documented in, the REMS system. It should be documented in the system. The patients should receive consistent, redundant information throughout the process. They should be given education tools to take home as well as the physician-patient agreement. They receive a medication guide at the pharmacy, and then there is a website accessible via the REMS system, call center access, and a survey."

Gallo said that communication tools need to be designed in a way that patients can understand, "Appropriate patients should not be discouraged from taking necessary medication because they are intimidated by the information. Information needs to be accessible, user friendly, and distribution should not cause a burden on the healthcare system or the patients."

The FDA's Dr. Throckmorton asked about the patient-physician agreements, saying that he has heard anecdotally that people don't pay much attention to them. He asked for some documentation showing that it works, and he asked about places where the physician in a long-term care facility might have a different relationship than a physician outside such a facility. Gallo said, "We need to look at those (approaches) which have been successful but also the ones that haven't, whether they scare the patient, or don't talk at all about why the medication is given. All that research on best practices needs to be looked at."

Standard Register. Dr. John Harden, a certified security consultant, said that prescription diversion such as forging and stealing the prescriptions of friends and family members can be stopped by **moving to a single REMS prescription format** similar to New York's controlled drugs system, which was successfully launched in 2007, "It is very effective in stopping this type of diversion…(I suggest) a REMS prescription. The patient would know, and the pharmacist would have an easy way to validate, that it is a valid prescription and not a counterfeit."

Dr. Harden's plan would:

- Allow only REMS-authorized prescribers to order.
- Validate the prescription control number at the point of sale.
- Document security features.
- Secure production and distribution.

He showed the audience a color forged prescription that he made in the hotel's business center by looking up some doctors' licenses and signing up for a free DEA look-up demonstration, "I could steal one from the doctor's office, or I could go on the web and order them…We need a way to allow only authorized prescribers to order. Every time an order is placed, the licenses need to be updated or checked. We also have a significant problem of dead doctor prescribing."

YNF. Phillip D'Alessandro, president/CEO, said **his company has a system** that can help with the new REMS. He said the REMS should:

- Include education for all stakeholders.
- Have retrievable enrollment information of all stakeholders which causes minimal impact on office routines and business practice.
- Be adaptable and scalable in all environments.
- Prevent non-enrolled patients from obtaining opioids.

According to D'Alessandro, YNF's solution – The Controlled Substance Authentication Verification and Education System (CSAVES) – doesn't impede patient access, doesn't require a new pharmacy system, is scalable with a current capability of 17 million transactions a day, and is business-rule driven and flexible to meet changing needs. The system includes a physician education program. When the doctor writes a prescription, he gives the patient a card kit with education information. The patient enrolls IVR (interactive voice response) or web and hears a safety message, then goes to the pharmacy and presents the prescription and card. The pharmacist enters the BIN number (part of the billing methods system), and enters the NDC number or patient information number. A transaction packet is forwarded to ProCareRx, where the business rules are applied and the card is checked for validity and to see if both the doctor and patient are enrolled. If no, a denial response is sent. If yes, the transaction is sent to the healthcare provider for approval, and the prescription is filled." D'Alessandro said that his system is in place in more than 99% of pharmacies.

Jennifer Bolen, founder of The Legal Side of Pain and the Pain Law Institute and former assistant U.S. attorney, said that **immediate-release opioids should be included** in the REMS under consideration.

Dr. Baruch Krauss, a pediatrician at Harvard Medical School and emergency medicine specialist at Children's Hospital Boston, advocated **ventilatory monitoring** for high-risk patients on oral opioids. He explained that the problem is that opioids are widely prescribed, and, in certain patients, they can cause life-threatening respiratory depression, especially in high-risk patients such as the elderly and the very young as well as post-surgical patients and adults and children with chronic diseases, such as pulmonary disease, cancer, or cardiac disease.

He pointed out that the most common life-threatening adverse event associated with oral opioid use is respiratory depression, and serious harm from respiratory depression is preventable, with patient safety enhanced by the use of ventilatory monitoring with capnography. Capnography is the non-invasive monitoring of exhaled CO_2 in the breath (nasal cannula in non-intubated patients). It provides the earliest warning for breathing problems and is sensitive.

Dr. Krauss recommended:

- Drug labeling should include a warning about respiratory depression.
- Ventilatory monitoring is warranted for all high-risk patients taking opioids.
- All stakeholders should be educated about the risk of respiratory depression.

Jane Maxwell, a research scientist at the University of Texas at Austin's Addiction Research Institute, said, "The **overriding metric is the number of deaths…and we have to get better data**. All deaths are reported to the National Center for Health Statistics (NCHS), but all opioids go into the category of 'Other Synthetic Narcotics,' and there is no way to determine which is which. The NCHS is developing a system to separate out the drugs reported as causing deaths."

Poison control centers have good data on cases called into them, but those deaths are a subset of all the deaths that occur. Maxwell said, "However, they offer one of the few examples that will tell us about the formulations, dosage units, the manufacturers, and reasons for use. This is a major database, and it needs to be online."

Maxwell said that the Inflexxion data do differentiate between opioids but have limitations, "Treatment data are a lagging data set, and there is an average of 10 years from age of first use to admission for treatment, so it won't be helpful in assessing new cases."

She also noted that some databases are proprietary to pharmaceutical companies, and some companies charge for databases, "The **proposed REMS needs to be transparent**, with all data available to researchers. It can no longer be a closed system. The methodologies used in new REMS need to be reviewed by expert panels, and those panel members need to be people who aren't receiving funds from the pharmaceutical companies."

Maxwell warned that addicted people in areas where OxyContin is being phased out are turning to heroin as the drug of choice, "We've created a generation of addicts, and who's going to pay the bill?"

Dr. Van Zee, the Virginia doctor, addressed the panel for a second time, saying that if there were to be a competency review for doctors, it should include competency for controlled substances in general. He cited the number of Xanax (alprazolam) pills that are prescribed every year. He also suggested **incentivizing sales reps based on markers for decreased abuse**.

FDA Ban on Unapproved Narcotics

The FDA announced on March 31, 2009, that it sent letters to nine companies that they had 60 days to stop manufacturing – and 90 days to stop distributing 14 different ***non-approved*** narcotics that were on the market. These were all high concentrate morphine sulfate oral solutions as well as immediate-release hydromorphone, morphine sulfate, and oxycodone. The companies were given 15 days to tell the FDA what they planned to do.

FDA officials emphasized that this was not a recall because existing product in the supply chain could still be distributed for 90 days and might still be sold after that time. They also insisted that the removal of the unapproved narcotics would not create a shortage for patients; patients would still have access to ***FDA-approved*** narcotics for pain relief, though they might have to switch agents.

The narcotics involved were all either tablets or liquid suspensions widely used to treat pain. The action does not include oxycodone capsules or cough medicines containing hydrocodone. One of the products involved represents 4% of the market for that type of product, while another constitutes 53% (fifty-three) of the market for its type of product.

FDA officials said the Agency was prepared to take enforcement action – which could include product seizure, injunctions (possibly with monetary penalties) or even criminal action – if the companies did not comply with the deadlines. Deborah Autor, JD, director of the FDA's Office of Compliance in the Center for Drug Evaluation and Research (CDER), said, "FDA expects all manufacturers and distributors to honor these deadlines, and we ***will not*** tolerate any sales or distribution after these deadlines."

The warning letters were part of the FDA's initiative on marketed unapproved drugs that was announced in June 2006. At that time, the Agency published a compliance policy guide describing its risk-based enforcement approach against illegally marketed unapproved drugs. Since them, the FDA estimates it has removed drugs from >200 companies. Dr. Janet Woodcock, director of CDER, said, "(These) warning letters are another demonstration of our commitment to remove illegal, unapproved drugs from the market." Dr. Autor added, "Drugs that pose safety risks are, and will continue to be, a high priority, for the FDA."

Were there adverse events linked directly to the narcotics being banned? Dr. Autor said, "We have adverse events for both approved and unapproved (narcotics). Our action is not because we feel these unapproved products are necessarily more dangerous than the approved drugs...but because they are not proven and appropriately-labeled, we don't know that their administration doesn't pose a risk for patients."

Then, on **April, 9, 2009, the FDA had to reverse itself**, allowing one product made by four companies (and distributed by seven companies) to remain on the market because it was deemed medically necessary, and there weren't sufficient alternatives. Dr. Throckmorton said, "We are amending a warning letter previously issued. We are sending letters to several manufactures and distributors of morphine sulfate elixir 20 mg strength, allowing them to produce and distribute that product until such time as we have approved product and there is sufficient supply. This action is taken to keep a medically necessary product available."

Dr. Throckmorton indicated that an outcry from the pain community led to the reversal, "The pain community and patients have helped us understand that there is a patient population, especially patients who require pain medication at the end-of-life for which (this medication) is medically necessary…We talked with the outside community as well, the pain medicine specialists, hospice care, etc...to understand the need for these products in that patient population, and we continue to look forward to working with them…to assure the medications are available…As a result, we have reversed the course we took and issued this letter…This interim solution will provide the means for 20 mg/ml morphine sulfate to be available."

Who are the patients who need 20 mg morphine sulfate elixir? Dr. Throckmorton said, "There is a population for whom these products are used where there are no other routes of administration that are useful, and they need to be able to hold the elixir in their mouth…They may not be able to swallow very well…So, if they have to take large volume (several hundred mg), that is enough where this high concentration is necessary …The other approved products are less concentrated and would require a higher volume of liquid in the mouth and would put them at risk for aspiration. It is an end-of-life population without other options."

This "reprieve" is temporary. Dr. Throckmorton explained, "The FDA is not withdrawing its action. We are modifying the timeframe the companies have to come into compliance… At the time we wrote the letter, we thought there were products to meet the needs of the pain community. After the letter was issued, we realized that was not the situation with these…Once an approved product is available, we need to assure ourselves and the community that the product is available throughout the U.S. in sufficient quantities and access... We won't take an action until 180 days after that approval of a morphine sulfate elixir or such time as other therapies are fully available and fully distributed to meet this need...and that will require us working with outside groups."

The reprieve is only for morphine sulfate. Dr. Throckmorton said, "We reviewed the evidence we have at present on those other products, and we don't believe the actions we've taken either caused or worsened any shortage of them."

The process of getting these drugs back on the market

The FDA's goal is not to ban the 14 unapproved narcotics forever – just to get them into approved status. Dr. Autor appealed to these and other companies with other unapproved products to **get their products approved**, "Companies have a responsibility to patients that they should actively pursue approval for their illegally marketed products."

The FDA is unlikely to accept claims that some of these drugs are exempt from the requirement to get approved. Dr. Autor explained, "Some of these drugs may claim to be grandfathered or legacy drugs…but few are likely to meet those criteria…If a firm claims its product is grandfathered, it is that firm's responsibility to prove that. There is no definition of a legacy drug, and unapproved drugs are not the legacy our patients deserve."

Companies Receiving Warning Letters About Unapproved Narcotics

Company	Drug
Boehringer Ingelheim/Roxane	Roxane oral solution 20 mg/ml Roxicodone tablets 5 mg
Cody Laboratories	Morphine sulfate solution IR 20 mg/ml
Glenmark Pharmaceuticals	Morphine sulfate tablets 15 mg and 30 mg Morphine sulfate solution IR concentration 20 mg/ml Morphine sulfate solution IR oral solution 20 mg/5 ml
Lannett Company	Morphine sulfate solution IR 20 mg/ml hydromorphone HCl tablets 2 mg and 4 mg
Lehigh Valley Technologies	Morphine sulfate tablets 15 mg and 30 mg Morphine sulfate solution concentrate 20 mg/ml
Mallinckrodt Pharmaceuticals Group	Morphine sulfate concentrate oral solution 20 mg/ml
Physicians Total Care	Morphine sulfate IR tablets 30 mg; hydromorphone tablets 2 mg Hydromorphone HCl tablets 4 mg
Roxane Laboratories	Hydromorphone HCl tablets 2 mg and 4 mg
Xanodyne Pharmaceuticals	Roxanol oral solution 20 mg/ml; Roxicodone tablets 5 mg

What is required for one of these drugs to get back on the market? FDA officials said most will be able to submit an abbreviated new drug application (ANDA) that includes chemistry, etc., simply showing bioequivalence and bioavailability without having to conduct new clinical studies. And FDA officials have indicated that, for these drugs, they would "commit extra resources and expedite review."

However, the proposed narcotic would have to go through the NDA process unless there is already an FDA-approved product (a reference product) on the market like it. If there is a reference product already approved, the new product can come in as an ANDA, and the process is the same – usually measuring blood levels of the narcotic. An official explained, "We do narcotic ANDAs, but sometimes the subjects take a blocking agent before the narcotic, so they don't have the narcotic effect for the particular product, and the blood level is measured without a narcotic effect."

Are clinical trials ever required as part of an abbreviated new drug application? Rarely. An official explained, "We have various methods to show bioequivalence. Most common – for tablets, capsules, and oral solutions – is *in vivo* testing in subjects, measuring levels of active ingredients to the active ingredient in the reference product. Each subject has to take a dose of each product, with washout periods, and the blood levels (of the active agent) compared. That is the standard way."

Where the active agent is not absorbed into the blood stream, where it can be measured reliably, as with topical products, bioequivalence may have to be established with a bioequivalence (BE) trial with clinical endpoints. This is a BE study because the analysis is for bioequivalence rather than efficacy. An official explained, "It is a bioequivalence trial, but, in essence, you get two groups of patients with the particular disease in question, and you apply the generic product in one group and the reference product in the other – and usually there would be a third group, a placebo, to make sure you have a sensitive test. You compare the clinical trial results in the two (drug) groups, and they have to meet certain bioequivalence criteria…So, it is a clinical trial in the context that you are testing disease patients and giving both the generic and reference drug but comparing the results, and your analysis is for bioequivalence, not for efficacy. It is not to see if the generic beats the placebo or the reference beats placebo, but whether the generic and the reference have equivalent efficacy and safety."

What happens if neither the generic nor the reference drug beat placebo? An official said, "That could happen if the reference weren't that effective. If the reference were tested many, many years ago and barely beat placebo (at that time) and the generic is not able to replicate that." Another official added, "We have had that happen, and we considered the study not sufficiently sensitive…It could be subtle differences in the populations or the way the trial was conducted." But in this case, the generic drug fails.

Does the FDA ever require any efficacy clinical trials for an ANDA? No, officials agreed. One said, "If we want the sponsor to show efficacy, it has to be an NDA."

Is the pathway for an ANDA different depending on the planned use – e.g., cancer vs. cough medicine, etc.? No. However, in bioequivalence studies for some cancer products, the FDA asks that the study be done in actual cancer patients rather than in normal volunteers because of the toxicity of some of the cancer drugs.

Are hydromorphone-containing cough medicines on the FDA radar? Dr. Autor said, "We continue to evaluate all the unapproved drugs on the market based on the risk based priority outlined in our policy guide…We have taken a number of actions…In September 2007 we did take a number of unapproved hydrocodone-containing cough medicines from the market for inadequate labeling to assure safe use."

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